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SPECIAL ISSUE ON ATOMIC MEDICINE

Guest Editor — LEE E. FARR

Chairman, Medical Department, Brookhaven National Laboratory

ATOMIC MEDICINE

PRESENT POSSIBILITIES AND LIMITATIONS OF THERAPY WITH RADIOACTIVE ISOTOPES — *Lee E. Farr*

THE MEASUREMENT OF RADIOACTIVITY IN RESEARCH AND CLINICAL MEDICINE — *E. E. Stickley*

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SOME ASPECTS OF TRACER THEORY — *Daniel C. Tosteson*

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CARCINOGENIC EFFECTS OF IONIZING RADIATIONS — *John T. Goduin*

THE EFFECT OF COBALT^{60} GAMMA RADIATION ON ANTIBODY FORMATION AND IMMUNITY — *William M. Hale and Richard D. Stoner*

THE TREATMENT OF THYROID CANCER WITH RADIOIODINE (I-131) — *Charles G. Foster*

CARBON-14 — *F. Marott Sinex*

ABSTRACTS

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from the current literature on serum and aortal lipid changes in atherosclerotic hens treated with adenosine-5-monophosphate

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Milch, L. J.; Redmond, R. F.; Calhoun, W. W., Chinn, H. I., and Cardiovascular Research Group, Federation Proceedings, Volume II, No. 1, Part 1, page 487, March 1952.

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EDITORIAL

Brookhaven National Laboratory

Lee E. Farr, M.D.

MEDICAL DEPARTMENT
BROOKHAVEN NATIONAL LABORATORY
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Brookhaven National Laboratory is one of three national laboratories established under the auspices of the Atomic Energy Commission. At its inception it was formed to explore peacetime uses of atomic energy, radiation, and radioactive isotopes, with emphasis on basic research. Brookhaven is operated by Associated Universities Incorporated, a nonprofit New York State educational corporation organized by nine northeastern universities which select representatives for the Board of Trustees. The Laboratory is comprised of the following scientific departments: Reactor Science and Engineering, Accelerator Project, Physics, Chemistry, Instrumentation and Health Physics, Biology, and Medicine.

The Medical Department, organized in its present form in the latter part of 1948, consists of six divisions: Physiology, Bacteriology and Virology, Biochemistry, Pathology, Industrial Medicine, and the Hospital. Included in the Physiology Division is the Biophysics Section. Twenty-four medical scientists form its present staff, together with about 120 others including nurses, technicians, and other assistants. The Hospital is a 36 bed hospital used for research purposes. Admission is by request from the attending physician and application from the patient together with all pertinent data upon which the staff bases its selection of those patients most suitable for study and treatment. The staff includes appointments of junior members interested in research who are appointed for one year. The appointment, however, is renewable. It is the purpose of these appointments to offer research opportunities to young men wherein they can work with experienced investigators on problems of interest to the Department and the Laboratory. These appointments range from those with clinical responsibilities to those concerned with the most fundamental problems of the various divisions of the Department.

Present Possibilities and Limitations of Therapy With Radioactive Isotopes

Lee E. Farr, M.D.

The present availability of radioactive isotopes for medical purposes has opened broad new fields for the development of procedures to diagnose and treat disease states. At the same time, by the very fact of these materials being radioactive, it has become imperative to delimit and define more precisely the long and short term effects of such radiation, in order that one hazard be not substituted for another. Until the parameters of safe usage of radioactive isotopes can be clearly demarcated, the use of these materials in medicine must be limited rather sharply. In the present discussion only the problems and advantages of *internally* administered isotopes will be considered.

When one speaks of therapy today with radioactive isotopes, he is speaking of tumor therapy, with the exception of treatment of hyperthyroidism and polycythemia vera. Probably the greatest potential advantage of internally administered isotopes is the possibility that by their chemical nature they will seek out and lodge within the tumor tissue, wherever that may be and in however diffuse and widespread a manner the growths may appear. As Ehrlich sought his "magic bullet" to destroy infectious agents, so many today are looking for its counterpart in radioisotopes for tumor control. Let us briefly examine the possibilities for such a compound.

One of the first radioactive isotopes used in medicine seems to fulfill these conditions. It is radioactive iodine. Thyroid gland tissue has a specific affinity for iodine which is selectively removed from the blood stream by the gland to be utilized by it in the manufacture of thyroxin. Although the capacity of the thyroid to remove inorganic iodine from the blood is not unlimited, the quantity of iodine presented to it at any time is generally small in relation to its capacity, so that a very effective clearance is obtained. This physiologic system therefore presents us with the most favorable situation for use of a radioactive isotope.

In those patients with hyperthyroidism in whom radiation treatment has been selected as the treatment method and wherein it is desired not immediately to destroy all functioning glandular tissue but only a portion of it, the use of radioactive iodine is most efficient. By making rough clinical estimates of the weight of the gland, which can be done by palpation, and relying upon this extraordinary affinity for iodine, it is possible to treat effectively this condition. When, however, we turn to a consideration of the treatment of thyroid carcinoma, we find that conditions are altered. Most tumors of the thyroid do not spontaneously take up iodine in quantities sufficient to achieve satisfactory therapeutic results. In a small percentage of patients, the tumor can be induced to take up necessary quantities of iodine after a period of physiologic stimulation by a drug such as thiouracil. This may require a regime of three months to up to two years before the desired effect is achieved. Because of the irregular form of the tumor, the

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geometry is seldom that which would be chosen for maximum effect. Further, we are dealing in this instance with metastatic tumors, for if there were only a solitary metastasis or the original tumor, this could be removed surgically. Although under stimulation the total uptake of iodine by the tumor will achieve concentrations making therapy worth while (70 per cent or more of administered iodine retained), the uptake of iodine is not uniform throughout all metastases. That is, one metastasis may take iodine up to saturation, whereas another will take up very little, so that net effectiveness of therapy becomes problematic, for unless all tumor cells are destroyed, the growth will continue and will spread from any remaining focus. To date at Brookhaven over a period of three years, we have seen a few instances in which isolated metastases were completely destroyed; that is, upon section no tumor cells could be found. But we have not been able to effect what we may term a "cure." Regression of soft tissue lesions is common and can be followed both by X-ray and inspection. In general, disappearance of roentgenologic evidence of tumor masses from lung fields has not been accompanied by disappearance of radioactivity over the lung fields following radioactive iodine administration after suitable physiologic preparation.

As has been pointed out by Dr. Foster in an accompanying article, the factor limiting the dose of radioactive iodine at the present time is its effect on the hematopoietic system. Unless specific protection can be provided to the hematopoietic system, this will remain an insuperable obstacle, for one must depend upon the blood stream to carry the isotope to all parts of the body where metastases occur.

From this discussion it is therefore evident that even under what may be considered as very favorable circumstances, it is difficult at best to provide sufficient therapy to hold tumor growth static or effect its complete destruction. The likelihood becomes small that using other radioactive elements for which tissues have very much less affinity, effective therapeutic doses can be delivered to the tumors without serious harm to other organ systems. Efforts are being made to circumvent this difficulty in a variety of ways.

Here at Brookhaven studies are under way using very short-lived radioactive isotopes, i.e., chlorine-38 with a half-lief of 38.5 min. When the malignant masses are so located within the body that they may be bathed with a solution containing a short-lived isotope injected into this region of the body, a high degree of local radiation is achieved. Because of the short half-life of the isotope, the quantity which escapes into the blood stream and

thereby to other parts of the body is held to a minimum. Thus, the radiation delivered to sensitive systems, such as the hematopoietic system, may be kept to a minimum and within the tolerance limits of that system. Such an approach will be of value in conditions wherein individual tumor masses are small and are distributed in a widespread manner, as over the peritoneum. Other variants of this basic approach are under investigation in this Laboratory.

Another and more revolutionary approach which is under investigation at Brookhaven is the production of radioactivity *in situ*. This may be done by previously providing a suitable element with a large capacity to capture neutrons, becoming radioactive as a result of such capture, and decaying almost instantly with development of radioactivity. It is desirable that a differential concentration exist between the tumor area and the surrounding normal tissue but this need not be nearly so great as in the case of a radioactive element. For example, in experimental therapy of glioblastoma multiforme in accordance with this approach, a relative distribution of capture element in the tumor area to normal tissue of 17 to 1 is considered quite adequate. This removes in some instances the requirement of specific uptake and permits one to take advantage of normal physiologic systems. Thus in brain tumor therapy one need not be concerned whether the capture element, boron-10 at present, be actually taken up selectively or not so long as its concentration in the extra- and intracellular water of the tumor area be significantly greater than its concentration in the extra- and intracellular water of normal brain tissue. In this instance the blood brain barrier is relied upon to keep boron out of normal nervous tissue, while in the tumor area it distributes itself throughout extracellular fluid presumably in the same manner as in parts of the body other than the central nervous system. By using the proper neutron flux for the proper time, it is thus possible to radiate selectively the tumor *in situ* with alpha particles emitted by the instantaneous decay of the boron after neutron capture. Elements other than boron can be used and the area to be treated, together with its physiologic characteristics, will determine the element to be used. This problem is now under intensive investigation at Brookhaven, the work having been started early in 1950. The problems presented by this approach are manifold and difficult. However, by using an element which emits alpha particles on disintegration, the problems of total body radiation are eliminated and the radiation is limited to the immediate area of the capture compound within the neutron beam, since the range of the alpha particle is measured in microns. The intensity of the radiation will be a factor of the concentration of the capture element, the neutron flux, and the time during which the area is exposed to neutrons. Throughout this discussion only thermal neutrons are referred to. Thermal neutrons are sometimes called "slow" neutrons as contrasted to "fast" neutrons, which have a very much higher energy and at the present time cannot be used in this fashion, since their reaction under these circumstances is different.

It is obvious that, by using the thermal neutron capture reaction to provide local radiation, many of the problems of total body radiation can be circumvented, since the range of the alpha particle is short and the half-life of the induced radioactive isotope is measured in a small fraction of a second. Under these circumstances it is impossible for the blood stream to carry the radioactive element to other areas of the body. It is true, however, that some activity will be induced in the elements which make up tissue, but

the total activity from such sources is small because of the low cross section of most body elements. Thus the potential radiation hazard is left within normal tolerance ranges.

From this discussion it appears that, with the exception of iodine in its relation to thyroid tissue, it is unlikely that one would find new single elements or compounds which would be taken up selectively by tumors to achieve a concentration, wherein the radioactivity would be great enough to be therapeutically effective. Compounds may exist which would be handled in this manner, but up to the present writing no one has isolated one nor even suggested a likely possibility. While radioactive isotopes can be used therapeutically in several diseases today, they do have severe limitations unless one is dealing with an element which has unique physiologic characteristics, and haphazard administration even of these isotopes is attended with considerable hazards.

The future of therapy with radioactive isotopes is attractive, but a great deal of work over probably a considerable period of time will be required to realize the existing potentialities. Most of the simple and most effective approaches to therapy with this class of compounds have already been explored and exploited. Progress from this point on will in all likelihood be slower but on firmer physiological bases than has been the case of many isotopes advocated more recently. It will require the close cooperation of the physicist, the chemist, the physiologist, and the clinician to bring forth knowledge which will permit advances into those areas of therapy looked for and sought for, but to date remaining elusive. That this will be done eventually I have no doubt.

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The Measurement of Radioactivity in Research and Clinical Medicine

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The detection and measurement of ionizing radiations is a necessary adjunct to clinical and research work using radioactive isotopes. Whether the work involves a tracer experiment, diagnostic procedure, or therapeutic use of radiation, physical instruments must be used to determine the amount of radioactivity present. It is the purpose of this discussion to describe the effects produced by radioactive radiations, and to tell how these effects are utilized in constructing sensitive measuring instruments.

Some radioactive elements are found among the elements occurring naturally in the earth's crust. Many others can be produced artificially, in the cyclotron or in the nuclear reactor. Whatever the source, the radiations which come out of radioactive isotopes are in the form of alpha, beta, or gamma rays. None of these radiations can be seen directly, but they do produce several effects suitable for detection and measurement technics. These include the photographic effect, luminescence, chemical effects, biological effects, and other ionization phenomena leading to electrical currents in gases. Neutrons also produce these effects, but neutrons are not emitted in ordinary radioactive decay. Nevertheless, neutrons are being used in medical research, and it is of interest to note the special methods for measuring them. This subject is of particular interest at the Brookhaven National Laboratory because of the specialized medical research which makes use of the unique facilities there.

Fundamentally, most of the effects resulting from the action of ionizing radiations seem to be manifestations of the same elementary phenomenon: the disturbance of the electronic outer structure of an atom or molecule. The observed result of this elementary disturbance is characteristic of the medium in which it occurs. If the ionization occurs in a gas where there is an electrical field between two electrodes, the ions of one electrical sign will be collected at one electrode, while the opposite electrode will collect those of the other sign. This is called an ionization chamber; the ion current output can be measured with a delicate electrometer. If a more intense electrical field is present, the ions will be accelerated and an electrical discharge may take place; some gases show this behavior much better than others. This phenomenon is used in Geiger-Mueller counters. In certain solids, the electronic rearrangements caused by a radioactive ray may result in a small flash of light—a scintillation—which can be observed by eye or counted by a special photocell. Related to this effect, some crystals will pass a momentary electrical current, and this can be used in what is called a crystal conduction counter. In certain chemical systems, radiation causes changes which can be measured quantita-

tively, making such systems useful as radiation dosimeters. The action of radiation on the photographic plate is at least in part due to this kind of process.

Historically, the photographic method was used earliest in the study of radioactivity. It was in fact the means by which radioactivity was discovered. It has been widely used since in many varied applications. Besides its many uses in dosimetry, it is a tool of greatest importance in studying patterns of distribution of materials in section, a method called radioautography, which is a complete subject in itself.

A device used in many early quantitative radioactive investigations was the scintillation detector. This was simply a screen coated with a fluorescent material, such as zinc sulfide, which emitted a tiny flash of light when struck by a particle issuing from a radioactive element. The spinthariscope was a simple improvement of this device, consisting of the screen with a microscope attached, enabling the observer to count flashes of light with more ease. At the present time a modern development of the same idea is becoming important as a detecting device. This is a scintillation detector in which the particles—or the equivalent flashes of light—are observed, not by the human eye, but by a photomultiplier tube, which converts the tiny flashes of light into electrical impulses strong enough to be counted by an electronic counting circuit. Fluorescent materials, called phosphors, especially sensitive to each of the types of radiation, including neutrons, have been discovered. As these phosphors and the photomultiplier circuits used with them continue to be improved, they may well become the most important equipment in the counting room.

Another simple device which has been used in a great deal of important work is the electroscope. The early instrument was based on the gold leaf device which is familiar from elementary physics demonstrations. After the electroscope is charged so that the leaves stand apart, if a radioactive source is brought nearby, the leaves are seen to fall, showing that the air in the electroscope is being ionized. The mechanism is simply that the ionization in the air neutralizes the electrical charges on the leaves. There is a more modern device based on this principle, the well known Lauritsen electroscope, in which the troublesome gold leaves are replaced by an extremely fine quartz fiber, having a thin gold coating. The principle remains the same: an electrical charge is put on the fiber, causing it to bend away from the framework which supports it, by the action of electrostatic repulsion. The position of the tip of the fiber is watched through a small telescope having a scale in its eyepiece. When the radioactive source to be measured is brought up, the ionization produced in the electroscope chamber allows a gradual neutralization of the charge, so that the fiber moves back toward the position where it rests when not charged. The rate of discharge is measured by timing the motion of the fiber across a selected portion of the scale. This rate is a measure of the strength of the radioactive source. In standardizing radioactive sources, some of the best measurements are made using this very simple device.

The Geiger-Mueller counter is the most widely used and the most familiar of the detecting devices employed in radioactive investigations today. It has many forms and variations. The essential parts are few: first there is an outer electrode, usually a cylinder of metal, although it may even be a thin layer of graphite painted inside a glass tube; the second element is ordinarily a fine wire stretched down the axis of the cylinder, acting

as the other electrode; the third element is the gaseous medium which fills the space between the two electrodes—this is the "counting gas," and many varieties are used, some being the radioactive sample itself, when it can be prepared conveniently in gas form. While the elements are simple, in many cases the construction of the counter is complicated by the requirements that the two electrodes must be held rigidly spaced with respect to each other, the "counting gas" must have a definitely controlled pressure and volume, and electrical connections have to be brought through the envelope to each of the electrodes. These problems have been solved in many ways, and there is a wide variety of commercially available counter tubes for all purposes.

In use, the Geiger-Mueller tube has to have a relatively high voltage between its electrodes. When this is provided, the passage of an ionizing particle through the sensitive space can cause the gas to "break down" and allow a pulse of electrical current to pass between the electrodes. This pulse is fed through an amplifier, from which it emerges with enough strength to operate an electrical counter. But for all this to transpire successfully, and reproducibly, many special requirements have to be made along the way. For consistent results, the high voltage supplied to the tube must be very constant, and this requires a highly refined source of power. Also, once a pulse is delivered

Mass Spectrometer in one of the Physiology Laboratories

into the amplifier, the counter tube must be "quenched," so that it will be ready to count when the next ionizing particle strikes it. The quenching is also necessary to prevent continuous discharge of the tube, which would result in its destruction. Quenching action can be provided either by judicious selection of the gas used to fill the tube or by special design of the electrical circuit which supplies the high voltage and takes off the signal. The latter method allows faster counting.

TYPICAL COUNTER ARRANGEMENT

The equipment of most laboratories doing research or clinical investigations with radioactive isotopes will include certain standard pieces of apparatus. The site of the actual measurement is usually a lead "pig" enclosing a sensitive Geiger-Mueller counter tube and a rack or sample holder which locates the sample in an accurately reproducible position. The purpose of the lead shield surrounding the counter tube and specimen is to minimize the interference of stray radiation from nearby experiments or other sources. The type of tube may vary to suit the particular kind and strength of radiation emitted by the isotope being used. Since most isotopes in general use are beta or beta-and-gamma emitters, thin-walled counter tubes are the rule. More sensitive tubes for weaker radiations have an extremely thin window. For the weakest radiations, there are counters with completely open windows which can be covered with the sample preparation while a constant flow of counting gas is supplied to the counting space within the tube.

The form in which the sample is prepared may also be varied to suit experimental conditions. Samples are sometimes made by soaking the liquid on blotting paper, or by evaporating it on small aluminum or plastic planchets. Some counters are made to take a special liquid sample cell shaped somewhat in the manner of a doughnut, the counter tube fitting through the center. Another highly useful counter tube is so constructed that an ordinary test tube containing the sample will stand upright in a well in its center. Radioactive materials which are convenient to handle in the gas phase may be pumped into a suitable counter tube, either alone or mixed with another gas to enhance the counting properties.

Following the primary detecting device such as the Geiger-Mueller counter, which produces a pulse when an ionizing particle passes through it, means must be provided to count the pulses occurring in a given period of time. The ideal pulse is an electrical signal of only a fraction of a volt lasting under a microsecond. That is to say, it is a momentary electrical current whose strength is less than a volt and has a duration of a part of a millionth of a second. This short time interval is necessary so that the detection of one particle will not interfere with detecting another which may follow very closely after the first. It is obvious that the signal is extremely feeble, and special means are needed to handle it.

For counting, therefore, the pulse is first put through an amplifier to increase its voltage to a more convenient value. In doing this, a great deal of stray electrical noise usually is amplified also, giving spurious signals which have to be weeded out. Special

amplifiers have been devised to perform this operation, and sometimes they are called on to perform other tricks of separation to distinguish between two or more types of radiation which may be present together.

In the counting hook-up, the amplifier ordinarily feeds its output into a scaling circuit. This device receives all the pulses delivered by the amplifier and counts them electrically. After a fixed number of pulses have entered the scaler, a single output pulse is released and passed on to an electromechanical register. A typical scale-of-64 circuit thus "scales down" the counting rate by a factor of 64, since it causes the register to record only once for every 64 pulses from the counter tube. Reliable scalers are made with factors of 2, 4, 8, 16, 32, 64, etc., or in decades, with factors of 10, 100, 1000, or even more.

When counting is done by means of scintillation detectors, similar electronic arrangements are provided. Much of the desired signal amplification is achieved within the photomultiplier tube in this case, however. The feature which makes this type of detector most convenient is the simplicity with which it can be modified to detect the different kinds of radiation. If alpha, beta, gamma, or even neutron measurements are to be made, it is only necessary to place on the tube the scintillating crystal which is particularly sensitive to the radiation to be detected. Of course, this is stated with an air of prognostication, since this ideal situation is not yet here; scintillating crystals are the subject of intensive search and study, so that future developments in the crystals and in the associated circuity should bring us close to this ideal after a period of years.

A few of the special types of detectors developed for clinical use deserve special mention. One of these is a Geiger-Mueller counter made in the shape of a probe. The sensitive volume of this counter is constructed inside a hypodermic needle, only slightly over normal size. Since the spacing between cylinder and wire electrodes in this counter is quite small, the "high voltage" supply need not be very great. All conditions contributing to mechanical and electrical hazard are thus minimized, and the counter probe can be used to explore within the body for sites where radioactive materials are concentrated. One such application is in the localization of brain tumors using radioactive phosphorus, which can be made to concentrate in the tumor area.

Another special device is a directional counter, built in such a way that it can "see" only a very narrow area. It is typically used in surveying restricted areas of the body to determine iodine uptake distribution and rate, in the test for analysis of thyroid function based on the administration of radioactive iodine. It may employ either the ordinary counter tube or the scintillation detector, surrounded by a mass of lead shielding which permits radiation to enter from one narrowly defined zone only.

There are many special applications where the ordinary tubes are useful, as in examination of the extremities for patency of the vascular system. In this the distribution of a tracer dose of a radioactive element is followed through the body to determine the best site for amputation in cases of injury, or to establish the extent of restriction in cases of circulatory disease.

Many of the methods for counting neutrons are adapted from the devices used for the ionizing radiations mentioned above. The neutron is not in its own right an ionizing radiation, but it does produce ionization effects by various indirect means. One way in which these two-step processes are utilized is in the boron-trifluoride

counter, a Geiger-Mueller tube in which the counting gas contains considerable amounts of boron. Neutrons react with boron and give rise to alpha particles, which are strongly ionizing and create a discharge in the counter. A boron coating on the counter walls has also been used to produce this effect. In other applications the counter walls have been coated with material such as uranium, which undergoes fission when activated by neutrons, with a resultant release of ionized particles able to trigger the counter. A method widely useful where the space distribution of neutrons is required is the use of foils of an element such as indium or gold, which are made radioactive under bombardment by neutrons. This induced radioactivity can be measured by the usual counting methods after the irradiation. This latter method is advantageous in animal and other experiments where it is desired to know the total neutron exposure over a period of time.

By way of summary, it is well to emphasize the wide variety of situations met in measuring radioactive isotopes. There is no single counting facility which can handle all cases. It is necessary to select from the battery of available counting tools an arrangement which best fits the particular isotope being used, considering the kind of radiation it emits and the intensivity level afforded by the experimental conditions. In addition, new instruments are developing constantly and often new methods must be devised for new situations.

Radiation Dosage in the Use of Radioactive Isotopes

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An estimation of the dose of radiation received by the tissues is important both in tracer and in therapeutic applications of radioactive isotopes. The methods for calculating the dose are the same for both uses, but the limiting factors are quite different. In tracer studies, which may involve normal subjects, the upper limit, or safe tracer dose, conforms to the accepted "tolerance" dose, a dose of radiation which will not produce any demonstrable ill effect. In therapeutic uses, the tolerance dose may be greatly exceeded, but it is necessary to keep the treatment from being worse than the disease, and serious effects are avoided by limiting the dose delivered to critical tissues, such as the bone marrow.

The amount of radioactivity administered is usually expressed in microcuries or millicuries, units which refer to the disintegration rate of the activity. The curie is defined for all radioactive substances except radium and radon (see Definitions on page 345) as 3.7×10^{10} disintegrations per second. The problem in dose estimation is to get from the units of disintegration rate to the units of radiation dose. This conversion depends upon an understanding of the physical processes involved.

Like X-rays, the "rays" from the various radioactive isotopes produce ionization as their energy is absorbed in air or in tissue. This ionization is associated with, but not entirely responsible for, the biological effects which result. However, it is more convenient to measure the ionization produced and to correlate the other effects with this than to try to measure other processes directly.

The dose of radiation which a tissue receives when exposed to X-rays is estimated from the amount of ionization produced in an ionization chamber under the same conditions. The unit for this dose is the roentgen, which is that quantity of X or gamma radiation which produces ions carrying one unit of charge of either sign in one cubic centimeter of air. (See Definitions for official definition.) This peculiar sort of a definition is required because what is desired is a measure of the amount of energy absorbed, and not necessarily a measure of the flux or the amount of energy passing through, which is much greater. It is also important to note that the roentgen refers to the energy absorbed in a unit volume, and is therefore an intensive, or point function, like temperature.

In other units, it turns out that the roentgen amounts to the absorption of about 83 ergs of energy per gram in air and to about 93 ergs per gram in water or soft tissue, the difference being due to the difference in chemical composition.

The roentgen is officially defined only for X and gamma rays. It has been agreed to base comparisons involving other types of radiation upon the energy absorbed in tissue rather than upon ionizations in air; so we come up with another unit called the rep, which stands for roentgen-equivalent-physical and which is currently used to mean the absorption of 93 ergs of ionizing radiation per gram of tissue. (An older definition used 83 ergs

per gram.) For X-rays, gamma rays, and beta (β) particles the biological effects for one rep are the same as those for one roentgen. Unfortunately, this is not necessarily true in the case of other ionizing particles, such as alpha particles, protons or neutrons, the biological effects per rep being somewhat higher by a factor of 2 to 20 for these heavier particles. It has not been possible to establish a biological unit such as the proposed rem or roentgen-equivalent-man because of large variations in effectiveness from tissue to tissue and the lack of a suitable universal biological indicator.

Almost all of the radioactive isotopes in use emit only β or β and gamma rays; so the rep suffices as a measure of the dose. The dose rate to a given tissue will vary with the concentration of the isotope in the tissue, and upon the energy and type of radiation emitted. When the concentration varies with time, a knowledge of metabolism is required which frequently can be obtained only through the use of radioactive tracers. However, reasonable estimates can generally be made in advance and over-exposure to radiation avoided.

The dose due to β particles is particularly easy to calculate if the tissue mass involved is large compared to the range of the β's. In general this range is only a few millimeters. When the assumption that the size-to-range ratio is large is made, it is seen that the dose can be calculated by considering that all of the energy of the particle is absorbed within the tissue; so the energy absorbed per gram will be proportional to the concentration of radioactivity per gram in a homogeneous system.

To get the instantaneous dose rate in rep/day from the concentration in microcuries per gram we multiply the number of microcuries per gram x the seconds in a day x the average energy per particle in mev x a factor converting mev per gram to rep. The answer to this comes out:

$$d = 54.5 C_t \overline{E} \quad \text{rep/day}$$

where d = dose in rep/day
C_t = concentration of radioactivity in microcuries per gram of tissue
$\overline{E}$ = average energy of the β particles in mev

One must be careful to use the average β energy; most isotope tables list the maximum β energy, which is usually about three times as great.

In general, the concentration of the radioactivity in the tissue is not constant during the period of interest. After reaching a maximum concentration, it falls off due to radioactive decay and due to metabolic processes.

If the fall-off is entirely due to radioactive decay, then $C_t = C\, e^{-0.693\, t/T}$ and:

$$d = 54.5\, C \overline{E}\, e^{-0.693\, t/T} \quad \text{rep/day}$$

where C = concentration at time zero, usually taken as the time of maximum concentration
t = time in days from time zero
T = the half-time of the isotope in days
e = 2.718. . . . , the base of the natural logarithms

If the removal by a metabolic process is rapid, compared to the rate of loss by decay, this process can generally be represented as an exponential and the metabolic half-time

substituted for T. Where the metabolic half-time is comparable to the radioactive half-time, the net half-time, $T = \frac{(Tm)\ (Tr)}{Tm + Tr}$. For example, the radioactive half-time for I-131 is 8.0 days, but in many cases the net or effective half-time in the thyroid gland is 6 days or less as the result of the combined decay and metabolic effect.

The dose delivered over a period of time is obtained from the expression for dose rate by the mathematical process of integration, which takes into account the variation of the concentration with time. This is expressed symbolically as:

$$D = \int_0^t (d)\, dt = \int_0^t (54.5\, C\overline{E}\, e^{-0.693\, t/T})\, dt$$

where D = dose in rep and the symbol $\int_0^t (\quad)\, dt$ means that the dose rate is integrated from time zero to time t.

The result for finite values of t is:

$$D = 78.6\, C\overline{E}\, T\, (1 - e^{-0.693\, t/T}) \quad \text{rep}$$

Or, if t is very long (seven or more times T):

$$D = 78.6\, C\overline{E}\, T \quad \text{rep}$$

The calculation of gamma doses is more complicated, because only a fraction of the energy released in this form is absorbed by the tissues. The dose rate due to a point source falls off approximately as the square of the distance from the source, and more precisely as $d = d_1 \frac{e^{-uR}}{R^2}$ where d_1 is the dose rate at a distance of one centimeter, R is the distance in centimeters to the point being considered and u is the linear absorption coefficient. For the gammas of energies ordinarily encountered u is approximately 0.03 $cm.^{-1}$ in soft tissue. That is, only about 3 per cent of the remaining gamma energy is absorbed per centimeter, and it takes about 23 cm. to reduce the intensity to 50 per cent by absorption. Instead of having a point source, however, we generally have the activity distributed throughout the volume in which we are interested. This is again handled by the mathematical process of integration, which here in effect treats each point as a point source and adds up the contributions from all points. The chief difficulties arise from attempting to express the shapes of irregular volumes mathematically. This is generally avoided by making simplifying assumptions such as regarding the trunk as a cylinder and the thyroid as one or two spheres.

The formula for gamma dose rate comes out:

$$d = IA\, C\, g \quad \text{rep/day}$$

where IA is the dose rate at 1 cm. from a point source of one microcurie and g is the geometry factor which results from the integration throughout the volume concerned. ($g = 200$ for center of trunk in average adult; $g = 20$ for 25 gram thyroid.)

When IA is not known it can be calculated from $IA = 54.5 \frac{0.03}{4\pi} f\, E$, rep/uc-day at 1 cm., where f is the fraction of the distintegrations which yield the particular gamma being considered and E is the energy of the gamma. Gamma rays are monoenergetic, so there is no confusion about average energies.

The formulas for accumulated doses are

$$D = 1.44\, IACgT\, (1 - e^{-0.693\, t/T}) \quad \text{rep}$$

and, if t/T is greater than 7,

$$D = 1.44\, IACgT \quad \text{rep}$$

Sometimes the use of the formulas involving $e^{-0.693}$ can be simplified by noting

that this is equal to $\frac{1}{2}$. Then $e^{-0.693\ t/T}$ becomes $\frac{1}{2}^{t/T}$ and, if t/T is an integer, the answer is easily obtained.

A few illustrative values are given in the following table:

Isotope	Half-time days	$\overline{E\beta}$	Gamma f E	(1A) rep/uc-day at 1 cm	Safe Tracer Dose* uc/kg
H^3	4500	0.0057	none		300
C^{14}	1.7×10^6	0.05	none		32†
Na^{24}	0.61	0.54	1 1.4	.41	1.5
			1 2.8		
P^{32}	14.5	0.695	none		2.4
I^{131}	8.0	0.205	.06 0.283		8.3**
			.76 0.363	.057	2.3‡
			.15 0.638		

* Based on 100 mrep in first 24 hours.

† See text.

** Thyroid geometry.

‡ Whole body geometry

Applications of the formulas vary from isotope to isotope, chiefly because of the variations in what is known or has to be assumed regarding their metabolism.

Sodium-24, for example, becomes distributed in the body's extracellular fluid space within a few hours after injection. The dose is usually calculated by assuming that sodium is uniformly distributed throughout the soft tissues. Since the radioactive half-time is so short (0.61 days), the effect of excretion in diminishing the dose is neglected. During the first day, 68 per cent of the total dose is accumulated.

Iodine-131 presents a strikingly different problem because of the selective concentration of iodine in thyroid tissues. Normal subjects may concentrate 25-30 per cent of the administered tracer in the thyroid, and hyperthyroids frequently concentrate over 50 per cent. In tracer studies, therefore, the calculations are chiefly concerned with the dose to the thyroid tissues and the dose to the rest of the body is of no consequence. Because the gland is so small, the geometry factor for gammas is also very small and the gamma contribution is only about 25 per cent of the beta contribution to the dose. Doses somewhat higher than "tolerance" doses are commonly used in thyroid work. If one assumes a 25 per cent uptake by a 25 gram thyroid, a tracer dose of 50 microcuries will give a maximum concentration of 0.5 microcuries per gram; this gives a radiation dose of over 50 rep to the thyroid. The importance of *in vivo* counting in thyroid studies and the resistance of the thyroid to acute radiation effects have been used as arguments to justify such a large dose of radiation. With the advent of more sensitive radiation detection devices, especially scintillation counters, it has become possible to count much smaller concentrations of activity than before and the tracer dose used in many clinics has been reduced to about 10 microcuries. In view of our ignorance of long-range consequences, such a reduction in dose seems to be desirable.

When I-131 is used to treat thyroid cancer, the quantities used may be 100-200 millicuries and the radiation dose to the rest of the body becomes significant. Of course it is desirable to give enough radiation to the cancer to destroy it, but this must not be at

Scientist in Hot Lab preparing 80 Curie Cobalt Source to provide Gamma Radiation for Use in Medical Department

the expense of producing, say, an agranulocytosis or an aplastic anemia. At least in so far as acute effects are concerned, the blood-forming tissues seem to be the most critical structures. In the case of iodine-131 this may be estimated from the dose delivered to the blood, which can be determined by measurement of the radioactivity in blood samples taken at various times after the dose is administered. Of course, if one waits till after the therapeutic dose has been given to make such measurements, it is too late; an estimate must be made from similar studies with tracers. One of the current research projects at Brookhaven involves determining the validity of such estimations.

Two more examples of the problems which come up concern the use of tritium (hydrogen-3) and of carbon-14. Both of these have long half-lives, so that the radioactive decay during an experiment is negligible. Early studies indicated that the metabolic half-time for the excretion of water was about nine days and the use of tritium as a tracer is generally based upon this as an assumption. In the case of carbon-14 the

combination of the long half-life and the possibility of its permanent deposition in bone have caused it to be regarded as a particularly hazardous isotope and stringent restrictions have been placed upon its use in humans. Work with animals indicates that this hazard has been overestimated and may be regarded as disappearingly small when the carbon-14 is given in the form of rapidly metabolized compounds. Actual experience with humans is required for an accurate assessment of this, however, and such experience is slowly being acquired within the limits imposed on the use of this isotope.

It is not practical for us to go through the periodic table and consider every isotope individually here. However, it is hoped that these remarks indicate at least the types of considerations which are involved in the use of isotopes and, if nothing else, show that having the formulas for converting concentrations of radioactivity to rep is only half the battle.

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DEFINITIONS

Alpha particles—Helium nuclei emitted in radioactive decay processes. These nuclei have a mass of 4 and a charge of + 2, and consist of 2 protons and 2 neutrons.

Beta particles—Electrons or positrons emitted in radioactive decay processes.

Curie—For radium and radon: That amount of radon in equilibrium with 1 gram of radium. For all other elements: The quantity decaying at a rate of 3.7×10^{10} disintegrations per second.

Erg—The unit of energy and of work in the centimeter-gram-second system.

Gamma rays—Electromagnetic waves originating in nuclear processes and generally of higher energy than X-rays.

Microcurie—10^{-6} curie; 3.7×10^{4} dps

Millicurie—$\frac{1}{1000}$ curie, 3.7×10^{7} dps

Neutron—Fundamental particle having mass of 1.0089 atomic mass unit and no charge.

Proton—Fundamental particle having mass of 1.0081 atomic mass unit and charge of + 1.

rep—The absorption of 93 ergs of ionizing radiation per gram of tissue.

Roentgen—That quantity of X or gamma radiation such that the associated corpuscular emission per 0.001293 Gm. of air, dry, 0°C, 760 mm. Hg. produces, in air, ions carrying 1 electrostatic unit of quantity of electricity of either sign.

Tolerance dose—Currently 300 milliroentgens per week. 100 milliroentgens per day may be allowed in isolated experiments.

X-rays—Electromagnetic waves produced when high speed electrons are stopped by collision with a dense target and by the consequent electron rearrangements in the target atoms.

Some Aspects of Tracer Theory

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During the past twenty years isotope tracer techniques have been applied to many biologic and medical problems. A tremendous literature on the theory and practical uses of such techniques has developed.[1,2,3] No attempt will be made to review this literature here; some general considerations, however, which bear on all tracer work will be discussed.

One might first ask the reason for the popularity of tracer techniques in biologic research. While biologic systems are not in thermodynamic equilibrium, they are often in or approaching a steady state. Setting aside thermodynamic formalities, it roughly holds that in the steady state the amount of each component in the system remains constant with respect to time. Most components of such a system are not truly static, but rather exchange or react with substances outside the system in such a manner that the rate of entrance or production of a given component equals its rate of removal or destruction. Two fundamental questions which must be answered in order to describe each component of a steady state system are: (1) What are its precursors and products? (2) What is the rate of exchange or "turn-over"?

In general, answers to these questions can be obtained either by disturbing the steady state or by using tracers. The limitations of the former technique and the advantages of the latter are well illustrated by considering the problem of distribution of sodium (Na) and potassium (K) outside and inside cells. For example, human red blood cells contain about 100mEq. of potassium per liter and 10 mEq. of sodium per liter, whereas the blood plasma contains about 4 mEq. K/l and 140 mEq. Na/l, and these values vary with time surprisingly little in the blood stream or under appropriate conditions *in vitro*. On the basis of experiments which had in common the characteristic of disturbing the steady state of the system, it was long believed that normally the surface of the erythrocyte was impermeable to these cations and became permeable only when the cell was injured. This was a justified deduction, because a net movement of K from cells to plasma occurred only when conditions (e.g., absence of glucose, exposure to cold or various hemolysins), which are probably injurious to the cell, were imposed. Furthermore, elevation of the concentration of K in the plasma caused little or no increase in cell concentration of K, so long as the plasma remained isosmotic with the cells. However, numerous experiments[4,5] with isotopic K and Na have provided incontrovertible evidence that the intracellular K and Na are constantly exchanging with plasma K and Na at an appreciable though fairly slow rate. Similar experiments have shown that comparable conditions obtain in almost all cells, although the actual rates of exchange vary widely.

Thus, question (2) has been answered relatively easily by the use of tracers in a

situation where non-tracer techniques proved difficult. Question (1) is trivial in this case, because the "precursors" of cell K and Na are plasma K and Na and vice versa, but this question becomes important in situations dealing with organic compounds. The frequency of problems comparable to that described above accounts for much of the popularity of tracers in biologic research.

It should be pointed out here that the value of tracers in biology is not limited to systems which are in the steady state. For example, since cellular K has been shown by tracers to exchange constantly with extracellular K, any deviation from this steady state (i.e., any change in the amount of K in the cells) must be due to inequality of the rates of movement of K into and out of the cells. Only by use of tracers is it possible to measure simultaneously each of these two rate processes.

We might next discuss the properties of an ideal tracer. Obviously it is desirable that such a substance possess chemical and physical properties identical with those of the substance to be traced. The degree to which this condition must be met depends on the use to which the tracer is put. Thus, to measure the total amount of water in a patient with the "tracer" antipyrine, it is only necessary that the antipyrine distribute itself uniformly throughout all of the body water, not that the kinetics of such distribution be identical with that of water itself. Although antipyrine has proved a useful "tracer" of water, it is clearly not as desirable as a substance which is chemically and physically identical with, but analytically distinguishable from, ordinary H_2O. It is for this reason that the oxides of deuterium and tritium, both isotopes of hydrogen, have been used to trace water. In general, such isotopes do satisfy the requirements of an ideal tracer.

The chemical and many of the physical properties of an atom depend on the behavior of the orbital electrons and hence on the nuclear charge. Isotopes of a given element such as hydrogen (protium, deuterium, and tritium) differ only in mass, not in nuclear charge or in the number and distribution of orbital electrons. However, there are certain physical properties of atoms which do depend on the mass. Thus, the viscosity of D_2O ("heavy water") is 25 per cent greater than that of H_2O at 20°C. Such differences can be significant in biologic systems since, for example, D_2O penetrates beef, rat,[6] and sheep[7] erythrocytes distinctly less rapidly than does H_2O. Such "isotopic effects" are rare, since the difference between the mass of two isotopes is generally small compared to the total mass of each. However, the fact remains that even D_2O fails to fulfill the criteria for an ideal tracer of water.

We will now consider the mathematical treatment of two of the many situations in which tracers may be used in biology. In particular, we will emphasize the number of experimental quantities necessary for solution of the equations. Certain symbols will simplify the treatment. These are: S = the amount of substance to be traced in a given compartment (the term compartment indicating anything from a "miscible pool" of molecules to a cell or tissue). R = the amount of tracer in the compartment. $\frac{R}{S}$ = the specific activity = a; t = time.

Case (1). One compartment open system — steady state
Model:

Conditions:

(a) At time zero the compartment is instantly tagged with an amount of tracer R_o.

(b) The amount of substance, S, in the compartment remains constant and, therefore, the amount coming in per unit time equals the amount going out in unit time (i.e., the system is in the steady state). These equal rates will be designated by the symbol ρ.

(c) The substance entering the compartment contains no tracer.

(d) The compartment is perfectly mixed.

The rate of change in the amount of tracer in the compartment must equal the difference between the rate at which tracer enters and the rate at which it leaves the compartment. In this case, the rate of decrease in the amount of tracer in the compartment equals the rate at which substance leaves the compartment times the specific activity in this substance. The specific activity in the substance leaving the compartment must equal the specific activity in the substance in the compartment at that instant, since perfect mixing is assumed. We may therefore write:

(1) $\frac{dR}{dt} = -\rho \cdot \frac{R}{S} = -\rho a$

(2) let $\frac{\rho}{S} = k$ = the fraction of S turned over per unit time.

(3) $\frac{dR}{dt} = -kR$ or $\frac{dR}{R} = -k\,dt$

(4) Integrating (3) and evaluating the constant of integration we obtain,
$\ln \frac{R}{R_o} = -kt$ or $\ln \frac{a}{ao} = -kt$ where R_o and a_o are the amount of tracer and the specific activity in the compartment at time zero.

Thus, in order to solve equation (4) for k, it is only necessary to measure R or a at the start of the experiment and at several later times. In order to calculate ρ from k it is, however, also necessary to measure S.

An analysis similar to this has been used in the study of uric acid metabolism in normal and gouty human subjects.[8] A known amount of N^{15} tagged uric acid was injected intravenously. It was assumed that this tracer uniformly tagged the "miscible pool" of uric acid, fulfilling condition (a) of the above model. Further it was assumed that the system was in the steady state (condition b) and that newly formed uric acid was not tagged (condition c). The last assumption was justified, because uric acid is essentially an end product and but little metabolized. By measuring the "specific activity" (actually the isotopic excess in this case) in the urine shortly after injection and at subsequent intervals, they were able to calculate k. Measurements made on urine rather than the blood were justified because urinary uric acid derives from the blood and at

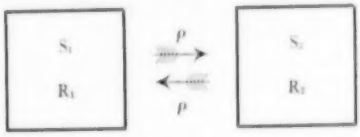
any moment (with but a slight time lag) has essentially the same specific activity as the blood uric acid. From a_0 and the known amount, R_0, of tracer injected, they were able to calculate S, the total amount of uric acid in the "pool" by the relation $S = \frac{R_0}{a_0}$. From S and k, ρ was calculated to be 700-900 mg. per day in the normal human male but 3 to 9 times that in gouty subjects.

A Scene in the Hospital Counting Room

Next, a somewhat more complicated system of two compartments, exchanging only with each other, will be considered.

Case (2). Two compartment closed system — steady state.

Model:



Conditions:

(a) Compartment one is tagged at time zero with an amount, R_0, of tracer. At that time there is no tracer in compartment two.

(b) The amounts of substance in compartments one and two, S_1 and S_2, remain constant with time, so that the amount of substance which goes from compartment one to compartment two in unit time equals the amount of substance going from com-

partment two to compartment one per unit time (i.e., the steady state obtains). Again these equal rates are designated by the symbol ρ.

(c) Both compartments are perfectly mixed.

Again it is clear that the rate of change in the amount of tracer in either compartment must equal the difference between the rates at which tracer enters and leaves the compartment. Thus, we may write:

$$(1)\quad \frac{dR_1}{dt} = \rho\left(\frac{R_2}{S_2} - \frac{R_1}{S_1}\right)$$

$$\frac{dR_2}{dt} = \rho\left(\frac{R_1}{S_1} - \frac{R_2}{S_2}\right)$$

By solving these simultaneous differential equations, we obtain the following expression:

$$(2)\quad \frac{R_2}{R_{2E}} = 1 - e^{-\rho\frac{(S_1 + S_2)}{(S_1S_2)}t}$$ where R_{2E} is the equilibrium value of R_2.

At the time T, when $\frac{R_2}{R_{2E}} = \frac{1}{2}$,

$$(3)\quad \frac{1}{2} = e^{-\rho\frac{(S_1 + S_2)}{(S_1S_2)}T} = e^{-0.693}$$

Therefore,

$$(4)\quad \rho = \frac{0.693}{T}\quad\frac{(S_1S_2)}{(S_1 + S_2)}$$

Thus, it is possible to estimate ρ by measuring the amounts of substance in both compartments, and the time required for the amount of tracer to reach one half of the way from its initial to equilibrium value in one of the compartments. This may be done in either of compartments one or two, since the half-time for exchange must be the same for both in this closed system.

A treatment very similar to this has been applied to the exchange of potassium between human red blood cells and "plasma" (actually the medium in which the cells are suspended) *in vitro*.[4,5] Similar work is in progress at the Brookhaven National Laboratory. Here compartment one was the "plasma" and compartment two, the red cells. Tracer (K^{42}) was added to the "plasma" (condition a). The fact that the measured amount of potassium in the red cells and "plasma" remained relatively constant with respect to time in these experiments fulfills condition (b) that the system be in the steady state. The amount of radioactivity in both red cells and "plasma" at various times was also measured, thus obtaining the "half-time" for exchange in two ways. It was found that human red cells exchange potassium at a rate of about 1.5 mEq./l RBC/hr. at 37°C.

These examples are but two of the simplest cases to which tracer techniques have been applied. It is hoped that they will serve to indicate some of the general principles of the method. It is important to realize that the number of measurements necessary to estimate the rates of exchange increases as the system becomes more complicated. Thus, for a three compartment system in the steady state, measurements of the amount of

substance in all three compartments, and the amount of tracer at various times in one compartment at least, are required. Even then the problem may be insoluble if the two exchange rates involved are approximately the same. A general treatment of multi-compartment exchange[9] is available to those who are interested.

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Industrial Medical Problems of Radiation

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The rapid advances in our knowledge and use of nuclear energy and the rapidity with which industry is finding new uses for radioactive isotopes have added a new challenge to the industrial physician. Besides the illnesses, the toxic agents, and mechanical injuries he has dealt with in the past, he is now concerned with an added problem—exposure to ionizing radiation hazards.

This problem is not an entirely new one. The familiar stories of the skin changes in the early X-ray workers, and the hazard from internal radiation found in the well known radium dial painters, make us realize this problem has been with us for some time though in a small and limited way.

Until the development of the atomic pile where large quantities of radioactive materials could be produced, the part played by radiation in industry was relatively small. Now, however, all major industries use radiation and radioactive isotopes to some extent. The amounts being used in industry are increasing by leaps and bounds, and it will not be long before a knowledge of radiation and its effect on people will be an important part of the training of all industrial physicians. The emphasis will and should be on the means of prevention of over-exposures. But no matter how well planned and organized a factory is, there will be the occasional unavoidable accident which must be dealt with. For this, an understanding of radiation decontamination procedures and care of injured personnel is imperative.

Radiation injuries may occur by exposure to a source outside the body or by exposure from a source that has entered the body through ingestion, inhalation, wounds, absorption through the skin, or other means. There are safe operating limits set forth for both external and internal radiation. Those for external radiation in general refer to total body radiation and not to a local area, such as the hands, which may be allowed twice as large a dose as that allowed for the total body.

The limits set for internal radiation depend on the type of material that has been ingested. Factors influencing these limits include the type of radiation—alpha, beta, or gamma, the physical and biological half-life, and the localization of the substance in the tissues. A substance giving off alpha rays is much more dangerous because of its greater ionizing power than is a beta or gamma emitter. The hazard from alpha particles is less than it might otherwise be, since the penetrating power of the alpha particle is limited to a matter of a few millimeters in tissue. Beta particles, which may penetrate a few centimeters into the body, may do serious local damage, but from the standpoint of whole body radiation may be less serious than gamma rays, which are strongly penetrating.

The hazard of a radioactive substance is influenced also by its physical and biological

half-life. The former is an immutable figure, characteristic of the specific substance. The latter depends upon excretion or retention in the body. Thus, a substance such as plutonium, which has a long half-life, localizes in bone, and is excreted very slowly, would have a much lower permissible dose than, for example, sodium-24, which has a short half-life and is rapidly excreted.

When exposure limits are exceeded, it is necessary to investigate the individual to determine what therapeutic measures may be appropriate and whether he should be allowed to continue at the work he is doing, thereby possibly endangering himself by added radiation or whether he should be removed at least temporarily from further exposure.

Areas where radioactive materials are handled must be constantly surveyed to see that no gross contamination develops which will result in unnecessary exposure. This is usually spoken of as area monitoring as against personnel monitoring, wherein the exposure to individuals working with radioactive materials is measured.

Individual exposures are determined by means of ionization chambers and film badges which are worn by people who may be exposed to radiation fields. The ionization chambers and film badges are examined periodically to measure the amount of exposure received by each worker.

At Brookhaven, area and personnel monitoring are functions of the Division of Health Physics, which distributes and processes the film badges and ionization chambers and keeps exposure records on all employees involved with radiation.

At an atomic pile site the radiation problems are one of the major concerns of the industrial physician. To protect the employee from injury, there is an elaborate medical program.

Initial or pre-employment physical examinations are done on all employees. The history includes a radiation history of work with radioactive materials and also a history of the number of diagnostic and therapeutic X-ray exposures each person has received. In the physical examination evidence of previous skin damage is looked for, and people who have had significant exposures to radiation, especially neutrons, are examined for evidence of radiation cataracts by slit lamp examination. Careful hematologic examinations are carried out. Yearly interval and termination physical examinations are done on all employees. Individuals who may be exposed to some special hazard may have more frequent or more specialized examinations, depending on the conditions being dealt with. If a person has an accident and inhales some toxic radioactive material, special examinations for determination of radioactivity in the stool, blood, or urine may be carried out. Repeated blood counts and other tests may be performed, depending on the type and degree of contamination.

Each employee has an initial and yearly chest X-ray. For those exposed to radiation in the course of their work, it is desirable to keep the exposure from diagnostic X-rays as low as is compatible with good medical practice. It is, therefore, necessary to know the exposures from the common diagnostic X-ray procedures. At Brookhaven the machines have been calibrated, so that the values may be determined for each roentgenogram. For their yearly chest X-rays, the scientific staff and those who may be exposed to radiation have a large 14 x 17 inch six-foot plate which gives an average exposure of 50 milliroent-

gens. Clerical workers and those not exposed to radiation hazards in the course of their work have a photofluoroscopic plate which gives about 1 r exposure to the chest. By the use of a cone, this exposure is fairly well limited to the chest area and is not considered as total body irradiation.

Contaminated personnel are handled in accordance with the type and degree of contamination. The majority of cases of external contaminations can be cleaned up with soap and water or some simple detergent. This can usually be done by the man himself and the need for medical care following this depends on the extent of contamination and the degree of exposure. Occasionally there will be a case in which these simple methods fail to remove the contaminating agent and other special methods, depending on the contaminating material, must be resorted to. Organic solvents which may cause penetration of the material through the skin are avoided as are harsh abrasives which might open avenues through which the material may enter the circulation.

Hydrochloric acid has proved to be of value in removing many of the contaminating materials that cannot be removed by the simpler methods. In practice a tenth normal solution is tried first and, if this fails to produce the desired effects, a stronger solution is resorted to.

The most common cause of internal contamination is through inhalation of radioactive materials. In these cases, the particle size and solubility of the contaminating agent are of importance. Slightly soluble particles may be inhaled and become fixed in the lung tissue. The soluble ones may be absorbed into the general circulation quite rapidly and, depending on the material, may be fixed in one or more tissues, or eliminated in the urine, stool, sweat, and other body secretions. The biological and physical half-life, as well as the type of radiation emitted from the contaminated material, is a factor which must be evaluated in any case of internal contamination.

A person who has inhaled radioactive materials is subjected to a routine of nasal irrigation through a rubber catheter inserted through the nose into the nasopharynx after the hairs guarding the entrance to the nose have been clipped away. These hairs generally catch considerable amounts of contaminating substance. Subsequently urine, stool and blood determinations are made to determine the extent of contamination and its effects.

Wound contaminations are cleaned and debrided. Amputation has not been necessary thus far, but one can conceive of situations where this might seriously be considered.

The treatment of ingested radioactive materials is similar to that of any ingested toxic material. They are removed by the conventional means of emptying the stomach and intestinal tract as quickly as possible and by the use of indicated antidotes.

Initially, the elimination of radioactive materials that have entered the general circulation is rapid, but when they have become fixed in the tissue, the rate of elimination is slow and quite constant and, under proper circumstances, may yield information as to how much is in the body. This rate of excretion may be increased to some extent by the administration of other substances that may replace or form soluble combinations with the fixed material.

This, in a very general way, furnishes an idea of the challenges and problems to be met by those who may choose to enter this field as industrial physicians.

Carcinogenic Effects of Ionizing Radiations

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In general, therapeutic agents may be harmful or beneficial depending upon the skill with which they are employed. This is particularly true of ionizing radiations and, in view of the tremendously expanded use of this agent in diagnosis and therapy, its tumor-producing potentiality will be discussed. Not only should this be of interest to you as a practicing physician in its application to patient care, but also from the standpoint of your own personal safety since exposure to radiations will be more likely in the years to come. Certainly this is not meant to detract from the use of radiation but merely to stress the potential hazard of this diagnostic and therapeutic agent.

Of the electromagnetic waves, i.e., gamma and roentgen or X-rays and the particulate radiations, alpha and beta particles, neutrons, deuterons and protons, the ones most commonly employed are the X and gamma rays and beta particles. Some of the radioactive isotopes presently employed in diagnosis and treatment such as iodine-131, phosphorus-32, iron-59, and gold-198 are largely beta particle emitters, although except for phosphorus they emit some gamma radiations. Many other isotopes are being employed in humans such as carbon-14, sodium-24, chlorine-38, potassium-41, strontium-90 and cobalt-60, some of which are strong gamma ray emitters.

Some use of neutrons is being attempted in the treatment of human glioblastoma multiforme at this laboratory and this will be discussed later.

It may be of interest to look briefly into the historic aspects of radiation. In 1792, George Adams in his book on electricity forecast the use of electrotherapy as presently applied to cancer. Röntgen in 1895 discovered X-rays, followed in 1896 by the discovery of radioactive rays by Becquerel. In 1934 it was discovered that radioactivity could be induced in stable elements. This knowledge has been put to extensive use as evidenced by the construction of uranium nuclear reactors (pile).

Within 6 months of the discovery of X-rays, the injurious effects of this tool were discovered in the form of an "X-ray burn." Other cases of roentgen dermatitis were recorded in the next few years. As early as 1902 the first case of roentgen carcinoma as well as the first fatality from this disease was reported in Germany. Eleven cases of skin cancer produced by X-rays were recorded by 1907. This stimulated animal experimentation in an effort to ascertain the effects of X-rays, which culminated in the production of a sarcoma in a rat by Clunet in 1910. This was enlarged upon by other experiments in which malignant tumors were produced in rats. The first actual roentgen carcinoma was produced by Block (1924) in rabbits. Since this time numerous experiments in a variety of animals have produced various neoplastic lesions such as pituitary tumors, thyroid carcinoma, ovarian tumors, lymphosarcoma, leukemia, skin carcinoma, and others. In humans, numerous cases of radiation-induced neoplasms have been recorded. Although the tumors have been predominately squamous and basal cell

carcinomas of the skin, instances of malignant spindle cell tumors of the dermis and subcutaneous tissues, rhabdomyosarcoma, sweat gland carcinoma, osteogenic sarcoma, and fascial fibrosarcoma have been observed. In addition, instances of oral and uterine cervical carcinoma developing several years after irradiation have been encountered. Occasional uterine corpus adenocarcinoma, rectal adenocarcinoma, and ovarian carcinoma are observed which suggest an etiologic relationship to previous irradiation therapy for lesions in adjacent structures. Martland extensively studied and reported numerous cases of osteogenic sarcoma induced in individuals who painted watch dials with a luminous paint containing small amounts of radium, mesothorium, and radiothorium. Instances of thoratrast-induced tumors of the liver and radon-induced bronchogenic carcinoma have been recorded.

In a busy hospital devoted to the diagnosis and treatment of cancer, radiation-induced malignant tumors are not infrequently seen. Examples have been encountered such as sweat gland carcinoma following the application of radium paste for dermatitis, squamous and basal cell carcinoma of the face following X-radiation for acne, fascial fibrosarcoma following irradiation for tuberculous nodes, rhabdomyosarcoma following irradiation for a metastatic testicular tumor, osteogenic sarcoma following irradiation for benign bone lesions and squamous carcinoma following X-radiation for dermatophytosis.

Numerous similar cases could be cited and indicate that iatrogenic radiation cancer is a real potential hazard in the use of radiation therapy. The interval between therapy and development of tumor is variable though usually long. In a series of radiation-induced human osteogenic sarcomas, the interval varied between 6 and 22 years. The dose of radiation in these cases was usually high and stated to be in excess of 3000 r delivered to the tissue, although one sarcoma developed after a tumor dose of 1550 r.

It appears that irradiated tissues are more likely to undergo cancerous change than non-irradiated tissues and that the higher the dose the greater the susceptibility to this change. The causative factors in the production of radiation cancers is not known, although various theories have been advanced as to the nature of the process. Some of these are chronic irritation, ischemia, cellular mutation brought about by direct action of radiations upon some molecular constituents of the chromosome, specific or non-specific, and primary or secondary chemical changes in the irradiated cells.

The histologic changes produced by ionizing radiations are not specific, inasmuch as similar changes may be seen following the application of heat, cold, electric currents, colchicine and podophyllin. There is, however, a pattern or combination of changes which when encountered enables one to be fairly certain that they are those induced by irradiation. These changes have been variously thought to be due to effects such as denaturation of nucleoproteins, inactivation of enzyme systems, and damage to protoplasmic colloids.

In view of the potential hazard of radiations, this laboratory has undertaken a long term study of the effects of small doses of Iodine-131 in rats. The doses employed are in the same range as those given for human hyperthyroidism. To date no instance of Iodine-131 induced human thyroid cancer has been encountered. The widespread use of isotopes in humans carries with it a great responsibility and its hazards should be

amply understood, in order to prevent the variety of iatrogenic radiation carcinomas seen during the past 50 years.

One of the more recent and interesting applications of particulate radiation has been the use of slow neutrons in the treatment of human glioblastoma multiforme. Prior to neutron bombardment the patient is administered borax intravenously which is concentrated in the tumor to a greater extent than in the surrounding brain. The patient is placed in position on the uranium nuclear reactor (pile) and the tumor area bombarded with slow neutrons which interact with hydrogen, nitrogen and boron with the production of gamma rays, protons and alpha particles, respectively. This then is the production of high energy radiations within the tumor which give up their energy over a short range (protons and alpha particles). This theoretically sounds like an excellent method for the production of high energy radiation within a tumor without injury to intervening structures or other parts of the body as with the systemic use of isotopes. This procedure has been used many times in the treatment of human glioblastoma multiforme, although it will be some time before the results may be evaluated. Extensive histologic studies are being performed from these cases as material becomes available.

As previously indicated, immediately following the discovery of ionizing radiations their harmful effects were not known but, as the knowledge of the destructive effects became apparent, protective methods were evolved. At present as newer and increased amounts of isotopes are produced, protective devices for handling and utilizing these substances are being developed in order to obviate the harmful effects of the radiations.

It is hoped that this brief discussion will stimulate an added degree of caution in the use of ionizing radiations, although at the same time not imply a lessening of their value. Its further potential usefulness in human disease is suggested in boron-slow neutron bombardment of glioblastoma multiforme as a specific example of many possibilities.

The Effect of Cobalt 60 Gamma Radiation on Antibody Formation and Immunity*

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A bibliography on the effect of X-rays on antibody formation is long and much excellent work has been reported. For a detailed bibliography the review by William H. and Lucy G. Taliaferro should be referred to (J. Immunol. 66:181, 1951). With the exception of the work of Hektoen and Corper using radium emanation, practically all the work on the effect of radiation on antibody formation has been done with X-ray. Therefore, it seemed worthwhile to study the effect of gamma rays from a cobalt^{60} source on antibody production, as well as their effect upon immunity. The radiation source was 21 pieces of cobalt arranged to give a uniform field at 12 inches, and the intensity of the radiation at the present time is approximately 600 rep per hour and the LD_{50} for 28 day old mice 750 rep.

We have obtained data showing that radiation does not reduce the level of influenza virus neutralizing antibody present at the time of irradiation and that it does not increase the rate of loss of passively administered antibody. Gamma irradiation of mice in the 24 hour period prior to the administration of influenza virus vaccine, or the 24 hour period after such an injection, is an effective inhibitor of antibody formation. In this work the secondary or anamnestic response has been used because this gives the maximum amount of antibody production in a short period of time.

Table I shows the effect of varying amounts of gamma radiation from a cobalt^{60} source on tetanus antitoxin production in mice. The Ehrlich type of titration was used and the titer is expressed in international units. Mice were bled to death from the heart 10 days following the secondary stimulus. The serum from each group was pooled and titrated as a single specimen. The primary response was produced by alum-precipitated tetanus toxoid. Fluid toxoid was used for the secondary stimulation. The mice in Group I were not irradiated and received both the primary and secondary stimulus, indicating the amount of antitoxin produced under such conditions. Group II received the primary stimulus only, serving as controls on the amount of antitoxin produced by the first injection. The remaining groups received the indicated amounts of radiation. It is obvious that 300 rep was not effective in inhibiting antitoxin production, whereas 475 rep was quite effective. The amount of radiation necessary to inhibit production of neutralizing antibody to influenza virus is similar to this.

* Based on a paper read before the American Association of Pathologists and Bacteriologists, New York, N. Y., April 11, 1952.

Because gamma radiation does not reduce the antibody level present at the time of irradiation, experiments were designed to test the effect of this form of radiation on passive immunity to pneumococcus Type III. A group of mice were given 650 rep of gamma radiation and 48 hours later passively immunized by the intra-abdominal injection of 0.3 ml. antipneumococcus rabbit serum which is 6 times the quantity of antisera necessary to protect against the amount of culture used. Another group of 40 mice were passively immunized in the same manner but received no radiation. Twenty-four hours after passive immunization, each animal received intra-abdominally 1/1000 ml. of a Type III pneumococcus broth culture. A third group of mice, neither irradiated nor passively immunized, received a like amount of culture, while a fourth group of 20 mice received radiation but no passive immunity or infecting dose. Of the animals not receiving radiation but passively immunized and infected, none died. Of the animals receiving the infecting culture only, all died. Of the animals irradiated, passively immunized and infected, 90 per cent died, while of those receiving radiation alone, none died. It appears that under the conditions of these experiments, 650 rep whole body radiation effectively destroys the protection normally conferred by the antisera.

TABLE I

Relation of Amount of Cobalt-60 Gamma Radiation to the Quantity of Tetanus Antitoxin Produced When Radiation is Given Just Before Secondary Stimulus

Group	No. of Mice	Radiation Dosage Given	Secondary Stimulus Given	International Units of Tetanus Antitoxin Produced
1	30	0	yes	17.50
2	30	0	no	0.20
3	30	300 rep.	yes	17.50
4	30	475 rep.	yes	3.75
5	30	575 rep.	yes	2.25
6	30	675 rep.	yes	1.00
7	30	775 rep.	yes	0.25
8	30	875 rep.	yes	0.20

In view of these results, an experiment was designed to test the effect of gamma radiation on the susceptibility of mice to pneumococcus mixed *in vitro* with an excess of specific antiserum. Three groups of 80 mice each were used. One group received 625 rep of cobalt^{60} gamma radiation, a second group received a mixture of pneumococcus Type III culture mixed with a tenfold excess of specific antisera, while the third group received 625 rep of radiation and three days later were given the culture-antisera mixture. None of the animals receiving only the culture-antisera mixture died, nor did any of those receiving only the radiation. However, of the animals receiving both radiation and the culture-antisera mixture, 75 out of the group of 80 died. It seems that again radiation has increased the susceptibility to infection.

Similar experiments have been done with tetanus toxin. There has been no essential reduction in the susceptibility of passively immunized mice to this toxin, nor does it reduce their susceptibility to neutralized or slightly underneutralized tetanus toxin. It seemed to us that the most logical explanation for this effect of radiation on immunity to pneumococcus infection was the resulting marked reduction in white cells and that possibly the resistance of irradiated and passively immunized mice might be restored by

whole blood transfusion from normal mice or by the injection of a suspension of leukocytes from normal animals.

The animals were irradiated 3 days before the challenge infection. The results we have obtained show that neither the white blood cells nor the whole blood transfusion was effective in restoring the resistance enjoyed by normal non-irradiated animals. We do not believe that this experiment should be considered conclusive by any means and feel that better methods of obtaining leukocytes may eventually enable us to restore the resistance of such irradiated animals.

In these studies we have tested some aspects not only of bacterial and viral immunity but also immunity to parasites for which we used *Trichinella spiralis*. In these experiments again an augmentation of the killing power of the parasites was found after irradiation. Infection of a group of 74 mice with 625 *Trichinella* larvae resulted in 7 deaths, whereas in a group of 40 mice similarly infected but irradiated with 550 rep the mortality was 80 per cent, while 650 rep given to a group of 33 mice increased the mortality to 100 per cent. No deaths resulted in 38 mice given only 550 rep of gamma radiation, while of 30 mice given 650 rep only 4 died. Again the results indicate that gamma radiation markedly interferes with the immune mechanisms.

To complete our studies we have also observed the effects of cobalt^{60} gamma radiation upon acquired immunity to *Trichinella spiralis*. Mice were immunized against the parasite by administering 100 *T. spiralis* larvae and then at an appropriate interval were given a challenge infection of 1,500 larvae. Of 34 mice immunized and receiving the challenge infection, 23, or 74 percent, survived. Of 39 nonimmunized mice receiving the same challenge, all died. Of 37 immunized mice which received 600 rep and then the challenge infection there were no survivors. This shows that this amount of radiation abolishes the active immunity produced by a previous infection with 100 *T. spiralis* larvae. In other studies in which the number of muscle larvae were counted in immunized and nonimmunized animals, it was found that gamma radiation exposure of the host resulted in an increase in the muscle larvae produced in both nonimmunized and immunized animals. The larvae counts were done four weeks after the challenge infection was given.

SUMMARY

Gamma radiation from a cobalt^{60} source significantly affects the immune mechanisms.

The Treatment of Thyroid Cancer with Radioiodine (I-131)

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In December 1941, Frantz and associates administered a tracer amount of radioiodine to a patient having osseous metastases from a follicular carcinoma of the thyroid gland. They noted that one of the metastatic bone lesions concentrated radioiodine. This was the first successful demonstration of radioiodine pickup by a thyroid cancer.

Subsequent investigations have clearly shown that only a relatively small number of all thyroid cancers collect significant amounts of radioiodine. In addition, the distribution of the radioiodine in the cancers is frequently nonhomogeneous. As a general rule, the ability of a given tumor to pick up radioiodine is closely linked with its morphologic type and the presence of colloid. Those tumors having a follicular structure and colloid show the greatest avidity for radioiodine, while pure papillary adenocarcinomas and less differentiated tumors have little or no avidity for radioiodine.

Because of the small number of patients who retained significant amounts of radioiodine when first seen, and since the effective treatment of thyroid tumors with radioiodine is dependent upon the selective concentration of the isotope by the diseased tissue, a search was made for a means to increase the avidity of the metastases for radioiodine. In 1948 Seidlin and associates reported on the induction of uptake of radioiodine in metastatic thyroid lesions by thyroidectomy, surgical or radiation, and by means of thyroid stimulating hormone. The rationale for these procedures is that, in a patient having both malignant and normal thyroid tissue, any administered radioiodine goes primarily to the normal thyroid tissue. The latter likewise competes successfully for the thyrotrophic hormone in the blood. Surgical removal of the normal thyroid tissue or its destruction by radioiodine removes this competition and allows the thyrotrophic hormone to act on the metastases. Moreover, the normal "braking effect" of the thyroid gland on the anterior pituitary gland is removed, and this causes an increased amount of thyrotrophic hormone to be produced. To these means may be added a third, namely, antithyroid compounds. These agents cause hyperplasia of the thyroid tissue and prevent the formation of thyroid hormone, resulting in an increased capacity on the part of certain functioning thyroid tumors to accumulate iodine. In our experience, total thyroidectomy (preferably by surgical means whenever possible), followed by the prolonged use of antithyroid compounds, has been the most successful way to date of inducing and increasing the avidity of certain thyroid carcinomas for radioiodine.

There are at least three important limitations to the use of radioiodine: 1) the natural lack of avidity of thyroid tumors for radioiodine and its nonhomogeneous distribution in the tumor, 2) the impairment of radioiodine collection by the diseased tissue following noncancerocidal doses of radioiodine, 3) the deleterious effects of

radiation on normal tissue. The means used to overcome the first limitation have been mentioned above. In regard to the second limitation, the metastases are not treated until they are retaining significant amounts of radioiodine, a state which minimizes the third limitation by concentrating the isotope in the tumor tissue, thus reducing the radiation dosage to non-thyroidal tissues.

Rawson and associates, with whom we are in agreement, believe that the following are indications for treatment of thyroid cancer with radioiodine:

1) that the tumor be not removable by a competent surgeon;
2) that the tumor be capable of concentrating sufficient radioiodine to exert a cancerocidal effect;
3) that the calculated total body irradiation delivered by the proposed therapeutic dose of I-131 be within the range of safety.

The present plan of treatment for patients with metastatic thyroid cancer is as follows. First, as much of the normal thyroid tissue, including adjacent tumor and regional metastases, as is possible is removed by surgical means. The patient is then given a tracer dose, 100 microcuries of I-131. If more than 5 to 10 per cent of the administered dose is collected in the region of the thyroid gland, this is presumed to be residual normal thyroid tissue and must be destroyed by means of therapeutic amounts of I-131 before satisfactory treatment of the metastases can be carried out. In the event of a medical contraindication to total thyroidectomy by surgery or its irremovability by this means due to technical reasons, the thyroid gland is destroyed by means of radioiodine. Following this, the patient receives a low iodine diet in addition to 0.5 Gm. of thiouracil three times daily. At intervals of about four to six weeks, I-131 tracers, usually in 100-microcurie doses, are administered following cessation of thiouracil therapy for 48 hours. The patient is scanned for evidence of activity in the metastases, and urines are collected for a period of 96 hours. If the cumulative urinary excretion in 96 hours is greater than 30 per cent of the administered dose, thiouracil therapy is reinstituted and the cycle repeated. When the patient retains 70 per cent or more of an administered tracer amount, he is deemed ready for a therapeutic dose. It is interesting to note that some thyroidectomized patients, whose retention of radioiodine is considerable, will state that they perspire more freely, need fewer blankets at night, and wear lighter clothing during the day despite the facts that they appear myxedematous clinically, have basal metabolic rates as low as -40 to -50, and protein-bound iodines well in the hypothyroid range.

Because the immediate limiting factor in the amount of activity which can be safely given to a patient is the effect on the hematopoietic system, an attempt is made to determine the roentgens-equivalent-physical (rep) which will be delivered to the blood by the therapeutic dose. This is done by administering an 800-microcurie dose and by determining daily over a period of seven days the activity of I-131 per ml. of blood. Utilizing this data and appropriate formulae, an estimate is made of the amount of activity which can be administered that will deliver about 500 roentgens-equivalent-physical to the blood. Although the aforementioned value is an empirical one, we have reason to believe that it is of the correct order of magnitude. One patient received 545 roentgens-equivalent-physical to the blood and developed a pancytopenia with subsequent uneventful recovery. A second patient at a collaborating institution developed a pancytopenia with subsequent recovery following 760 roentgens-equivalent-physical

to the blood. The writer knows of one patient who died of aplastic anemia following 1,300 roentgens-equivalent-physical to the blood. To date we have been able to accurately predict the roentgens-equivalent-physical which will be delivered to the blood by a therapeutic dose calculated on the basis of a tracer dose in only 25 per cent of a small group of patients so studied. Since we consider this a very important consideration, further studies are being done to increase our prediction accuracy.

With single therapeutic doses ranging between 50 and 254 mc., regularly-occurring effects on the formed elements of the peripheral blood have been found. The most sensitive cells are the lymphocytes. If the fall in circulating lymphocytes is plotted against the number of millicuries administered, a good correlation is not obtained. However, if the former is plotted against roentgens-equivalent-physical delivered to the blood, a good correlation is obtained. A decrease in total leukocytes is also regularly observed, but the changes are later in time and less marked. No cases of bleeding due to thrombopenia have been seen by us, but in one patient an anemia of sufficient severity to warrant several blood transfusions was observed.

When single therapeutic doses in excess of 100 mc. are administered, nausea and vomiting are not uncommonly seen and are believed to be manifestations of radiation sickness. In some instances it is severe enough to require the administration of parenteral fluids. To date we have not noticed the onset of irradiation sickness after 14 days following the therapeutic dose. Temporary amenorrhea, herpes zoster, and temporary epilation of scalp hair over a metastasis have also been observed. In patients with osseous metastases, there is usually an exacerbation of the bone pain during the first week following therapy. Thereafter, the bone pain is considerably relieved. In no instance have we observed calcification of bony lesions following treatment. Patients with pulmonary metastases will sometimes complain of chest discomfort in the form of a drawing or sticking sensation, particularly on deep inspiration. In several instances by roentgenograms, we have observed considerable reductions in the size and number of pulmonary metastatic lesions as well as soft tissue lesions in other parts of the body. Although no case of clinical hyperthyroidism has been observed by us following therapeutic amounts of radioiodine, protein-bound iodine levels in the hyperthyroid range have been noted. In a few instances, workers at the Memorial Hospital in New York have isolated what seems to be thyroglobulin from the blood following a large therapeutic dose. This has been interpreted as being indicative of massive tumor destruction with release of thyroglobulin into the blood stream. In one patient we have observed increased growth in the tumor simultaneously with its increased avidity for radioiodine. In several patients we have studied the effects of I-131 on kidney function. This was done by means of para-aminohippuric acid clearances, sediment tests, concentration tests, and urea clearance studies. In no instance did we find any significant difference between pre- and post-irradiation values.

In summary, radioiodine 131 has a useful, although presently limited, role in the therapy of metastatic thyroid cancer. When its indication and limitations are kept in mind, beneficial results can be obtained. Our procedures for the preparation and treatment of patients with this isotope have been given briefly, as well as some clinical observations following its use.

Carbon-14

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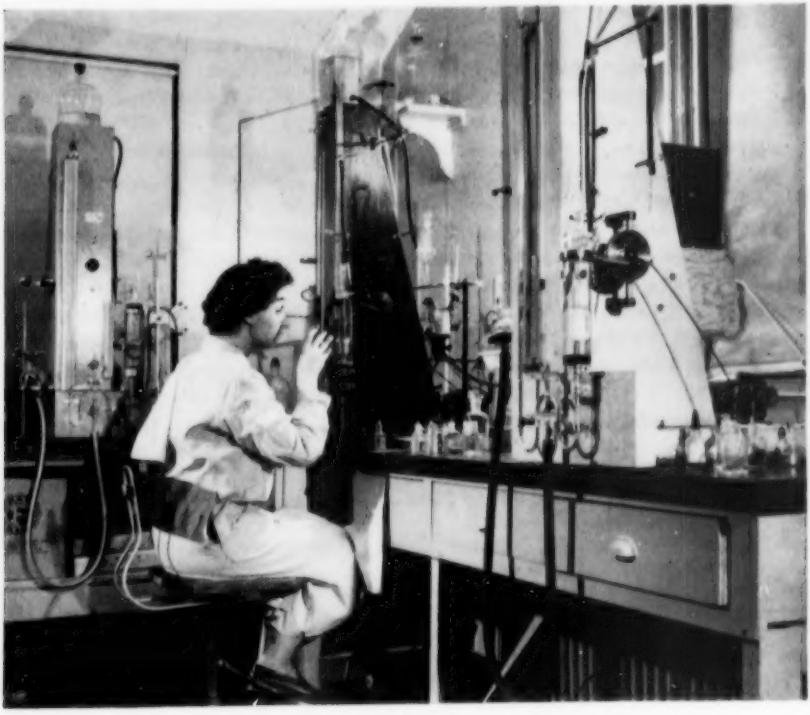
The chemistry of animals and plants is primarily the chemistry of carbon compounds. Because of this an isotope of carbon, carbon-14, occupies a unique position among isotopes of interest to the biochemist. Carbon-14 is radioactive and in any material containing this isotope, one half of the carbon-14 atoms present will in the course of 5,600 years emit negative beta particles from their nuclei and become nitrogen-14 atoms. With appropriate apparatus the number of such disintegrations occurring per minute can be measured and the amount of carbon-14 present determined.[1]

The simplest compound of biological interest which can be labeled with carbon-14 is carbon dioxide. $C^{14}O_2$ has been used in a number of investigations of the carbon metabolism of bacteria, plants, and animals. The steps by which plants reduce carbon dioxide to carbohydrate during photosynthesis have challenged several generations of biochemists. Labeled carbon dioxide has made it possible to explore the initial fixation process.[2] Plants have been exposed to an atmosphere of $C^{14}O_2$ for a very brief interval of time. The chemical constituents of the plants have then been fractionated and examined for carbon-14. A high concentration of carbon-14 in any substance has been taken as an indication that it is closely associated with the primary fixation process. A surprising finding in work with animals is that carbon from CO_2 is also incorporated into the organic compounds of mammalian tissue, particularly those of liver, and that the chemical reactions involved are quite similar to those which occur in plants.[3] The carboxylation of pyruvic acid to form the four carbon acids, oxalacetic and malic, is now known to be an important physiologic process for both plants and animals. Other aspects of $C^{14}O_2$ metabolism in animals have been studied. Studies on the deposition of carbonate in bone are providing useful information concerning the nature of bone growth and replacement. The rate at which C^{14}-bicarbonate is expired as $C^{14}O_2$ has been measured, contributing to our understanding of respiration.[4]

We have already mentioned how $C^{14}O_2$ is used to follow photosynthesis. If the plant is exposed to labeled $C^{14}O_2$ over a long period of time, the whole plant becomes labeled with carbon-14, and it is possible to isolate from such a plant sugars in which the carbon chains are uniformly labeled with carbon-14. Carbon-14 labeled glucose can be obtained in this manner and used to study the glucose metabolism of animals. By injecting carbon-14 labeled glucose into normal and diabetic rats and dogs, it has proved possible to relate quantitatively glucose production and glucose utilization in such a manner that it is no longer necessary to speak of "overproduction vs. underutilization of glucose" in vague terms.[5] Similar techniques should clarify many difficult problems in which the rates of competing physiological processes vary.

Similar experiments may be carried out with labeled amino acids and labeled lipids. To carry out such an investigation, a few millicuries of carbon-14 as $BaC^{14}O_3$ are obtained from Oak Ridge and then incorporated into the compound to be studied. Once

a compound is labeled with carbon-14 a number of avenues of investigation are open. Its oxidation can be followed through the appearance of $C^{14}O_2$ in the expired air. Its urinary and fecal excretion can be determined without recourse to any special analytic procedures other than counting techniques. In the case of amino acids, incorporation into protein can be measured and estimates made of the rates of protein synthesis, replacement, and breakdown. If desired, labeled proteins can be isolated and their metabolism followed in turn.[6] The exact metabolic pathways taken by carbon atoms in the synthesis and metabolism of the individual amino acids can be followed. For example, glycine has been found to be an important unit in the formation of hemoglobin, and carbon-14 labeled glycine has been used in investigating the mechanism of the synthesis of heme.[7]



A Corner of the Biochemistry Laboratory

In lipid metabolism, carbon-14 labeled cholesterol is now being used to study experimental atherosclerosis. Carbon-14 estrone and testosterone are available for the study of intermediary steroid metabolism. In the field of pyrimidine and purine metabolism, specific carbons of the purine and pyrimidine skeletons can be shown to originate from serine, glycine, acetate, formate, or CO_2.[8] Orotic acid, 4-carboxyuracil, has been

shown to be an active precursor of the urydilic and cytidylic acids of nucleic acid pyrimidines.[9] From these experiments new sequences or reactions have been proposed for the synthesis of molecules of nucleic acid. In the plasma extender program of the National Research Council, "blood substitutes" such as polyvinyl-pyrrolidine and dextran have been labeled with carbon-14 in order to follow their retention and metabolism. The information obtained has proved very useful in tailoring molecules to meet the desired specifications.

An unusual and clever application of carbon-14 is its use in determining the age of biologic material. As a result of cosmic ray bombardment, the atmospheric carbon dioxide contains about 10^{-10} mg. of carbon-14 per 100 mg. of carbon. Since the carbon of all living organisms is ultimately derived from the CO_2 of the atmosphere, the carbon of all living things has this concentration of carbon-14. When the organism dies, this carbon-14 begins to decay. By using refined techniques for the counting of carbon-14, it is possible to determine the years which have elapsed since any sample of carbon was part of a living organism. Needless to say, this is of great value to the anthropologist.[10] Any recent issue of the Journal of Biological Chemistry will provide further examples ofthe use of carbon-14 in biological research.

Experiments carried out in animals can be expected to make significant contributions to medicine; however, giving a patient carbon-14 for diagnostic study presents some rather unique problems. The half-life of carbon-14 greatly exceeds the life span of the individual; therefore, isotopic decay cannot be relied upon in calculating retention and radiation dosage. Instead, it is necessary to estimate retention and radiation on the basis of previous experiments on animals. Each individual carbon compound, therefore, constitutes a special case. The accumulation of sufficient data to permit more liberal administration of carbon-14 to human subjects will be slow, but progress is being made.

Carbon-14 work is not an end in itself, but rather an extremely useful addition to the armamentarium of the biochemist and physiologist which must be used in conjunction with the other skills and techniques in order to gain an understanding of the chemistry of living things.

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206. *Late Lymphatic Leukemia Complicating Hypersplenic Syndrome*, HERBERT A. COCHRANE AND LUDWIG GROSS, St. Vincent's Hospital, Staten Island, N. Y. Arch. Int. Med. *89*:82-89, January 1952.

In the case reported, the patient, a woman fifty-two years of age, showed signs and symptoms of hypersplenism, which were completely relieved by splenectomy. She remained well for more than a year and then was found to have chronic lymphatic leukemia. Serologic tests for syphilis were positive, but there was no clinical evidence of the disease, nor any evidence that the hypersplenism was of syphilitic origin. It is suggested that an increased hormonal activity of the spleen was induced by some unknown stimulus; by removal of the spleen, this organ's large collection of reticuloendothelial cells was also removed, but splenectomy did not eliminate the unknown primary stimulus, which continued to act on the remaining reticuloendothelial system, possibly genetically predisposed, affecting the balance of "acting substances" and eventually resulting in lymphoid metaplasia. This is a "speculative conception" of this case, but it can be correlated with Wiseman's theory in regard to the role of the reticuloendothelial system in the production of leukemia. 19 references, 4 figures.

207. *Banthine in the Treatment of Duodenal Ulcers*, JOE E. HOLOUBEK, ALICE BAKER HOLOUBEK AND RICHARD B. LANGFORD, Shreveport, La. New Orleans M. & S. J. *104*:173-76, November 1951.

This series of cases includes 40 patients with duodenal ulcers treated with banthine which had been previously reported, and 36 additional cases which had not been reported before. In all cases the symptoms were suggestive of duodenal ulcer and this was confirmed radiographically in every case. Treatment consisted of a very liberal diet plus banthine 50 mg. every 6 hours. A few of the early cases received 100 mg. every 6 hours, but the smaller dose was used throughout the latter part of the study. In addition, some of the patients were given anti-acid therapy between meals and at bedtime.

There was marked relief of symptoms in nearly every case, and improvement was very striking in the larger portion of cases. Most of the patients remained on banthine therapy for less than 3 months, and 4 stayed on treatment for 6 months. Healing was demonstrated radiographically in 26 of the patients. We were unable to obtain follow-up x-ray studies on the remainder.

It was interesting to note that a very large percentage of these patients were semi-skilled and unskilled laborers, and only a small percentage were executives. Sixteen of the 76 patients developed recurrences, but in every case they became symptom free rapidly after the institution of banthine therapy again.

It is our impression that banthine is a very effective anti-spasmodic in the treatment of duodenal ulcers, but it in no ways alters the indications for surgical therapy and is not capable of preventing recurrence. 7 references. 7 tables.—*Author's abstract.*

208. *Pulmonary Mycosis. Clinical and Pathological Features.* R. ELO, R. PATIALA, AND V. RITAMA, Helsinki, Finland. Ann. Med. Int. Fenniae. *40*:99-116, 1951.

The writers report three cases of pulmonary mycosis, the first of which can be said to have been acute, the second subacute, and the third chronic. The two former were caused by *Actinomyces bovis*. In the third case, in which no certain diagnosis could be made while the patient was alive, the course of the disease resembled tuberculosis. At autopsy blastomycotic lesions were present as evidenced by the tissue reaction and the presence of yeast-like bodies. The micro-organism cultivated from a pulmonary lesion however was classified, on the basis of its growth properties, its morphological features and pathogenicity, as *Candida albicans*. 9 references. 10 figures.—*Author's abstract.*

Pulmonary mycoses are being recognized more frequently since the widespread use of antibiotics. Many are superinfections, but others are now revealed when the acute bacterial component is controlled with antibiotic therapy—Editor.

209. *Early Diagnosis in Massive Gastrointestinal Hemorrhage.* NORMAN ZAMCHECK THOMAS C. CHALMERS, MAX RITVO, AND MELVIN P. OSBORNE, Boston Mass. J.A.M.A. *148*:504-07, Feb. 16, 1952.

Prompt diagnosis of the cause of massive upper gastrointestinal hemorrhage may be facilitated by the usual history and physical and laboratory examinations, aided by emergency roentgen examination. The prompt recognition of patients bleeding from esophageal varices is expedited by use of the sulfobromophthalein sodium liver function test and esophagoscopy and balloon tamponade. Early diagnosis of the cause of bleeding expedites selection of patients requiring surgical intervention. Properly applied, this diagnostic regimen is advantageous for use at the large municipal hospital and may be of benefit wherever appropriate facilities and trained personnel are available. 10 references.—*Author's abstract.*

210. *Alpha Streptococcus Meningitis. Report of a Case Successfully Treated with Chloramphenicol.* ROBERT C. HAGAN, JEROME E. COHEN, AND CARL EBELING, Baltimore, Md. Antibiotics and Chemotherapy *2*:147-51, March 1952.

Meningitis caused by alpha Streptococcus (viridans), for which no apparent portal of entry can be ascertained is uncommon. This report presents the findings in a patient with this type of meningitis in whom there was a rapid recovery following chloramphenicol therapy.

The patient was a 59 year old, white, male who had been in good health until four hours before admission when he developed a severe, generalized, unrelenting headache associated with nausea and vomiting. When brought to the hospital he was delirious and completely unmanageable, with a temperature of 101.4° F, a pulse of 90, respiration of 24 and a blood pressure of 140/70. Except for classical signs of a purulent meningitis, the physical examination was unrevealing. The laboratory results included a 40,600 leukocytosis, spinal fluid cell count of 16,000 with a protein of 415 mg. per cent and a sugar of 2.5 mg. per cent. X-rays of the sinuses were negative and those of the skull revealed a well healed fracture of the left frontal bone (sustained two years previously). Direct smear of the spinal fluid revealed numerous gram-positive cocci and the culture was positive for alpha Streptococci.

Therapy consisted of 1 Gm. of chloramphenicol intravenously and 2 Gm. intramuscularly, followed by 1 Gm. intramuscularly every 12 hours. The improvement in 24 hours was striking. On the 5th day he had an exacerbation. He was then placed on the oral form of the drug and the temperature returned to normal levels in four hours and the improvement from then on was rapid and progressive. He received therapy for a total of nine days. 6 references. 1 figure.—*Author's abstract.*

211. *Cortisone In The Treatment of Tetanus: Report of Case.* NORMAN A. CHRISTENSEN, HADDOW M. KEITH, LUCIAN A. SMITH, NORBERT O. HANSON, AND DONALD E. RALSTON, Rochester, Minn. Proc. Staff Meet., Mayo Clin. 27:28-32, Jan. 16, 1952.

Although foci harboring Clostridium tetani usually can be effectively eliminated by débridement and proper care of wounds, along with administration of antibiotics, no means yet at hand will break the combination and neutralize the potent tetanus exotoxin once it has united with the central nervous system. Tetanus antitoxin given intramuscularly, intravenously, or both, in adequate amounts can be expected only to neutralize the uncombined exotoxin yet in the tissue fluids and that produced until the focus of infection is eliminated. Yet tetanus is a self-limited disease. If the patient is able to survive the critical first two weeks, his chances of recovering completely within a total of three to five weeks are usually excellent.

In the absence of any effective agent that will reverse the disease process or speed the immune reaction therefore, and because exhaustion is frequently the only apparent cause of death of many of the patients, a new approach to the problem was considered. Others had reported good results from the use of cortisone and ACTH in a variety of diseases. The underlying reasons for the effects they had obtained might apply, we thought, in tetanus. Accordingly, we determined to ascertain whether cortisone or ACTH might help in treatment. The substances named would be used as adjuncts of the presently accepted treatment, not as substitutes for it. Tetanus could then be considered in light of Selye's adaptation syndrome. Cortisone and ACTH might also have an attenuating or prophylactic effect against serum reactions when tetanus antitoxin in horse serum was used in rather large amounts.

Undesired side effects with cortisone may occur but the likelihood of their appearance is reduced if the preparations are used for a relatively short period. The side effects can be controlled by regulating the dose of the hormones. Contraindica-

tions to the use of cortisone and ACTH in tetanus are the same as in other conditions. The possible benefits have to be weighed against the possible risk to the individual patient. Use of the preparations would not be indicated in mild cases of tetanus.

On June 30, 1951, a white farm boy, aged 4 years, suffering from tetanus, was admitted to the hospital. Administration of tetanus antitoxin and antibiotics, and other generally accepted treatment, were started at the time of his admission. At the end of his first day in the hospital (fourth day of his disease), his condition was considered critical. Trismus, opisthotonos and tetanospasm were severe enough to threaten his life. At this point, administration of cortisone was started: 25 mg. every eight hours. After two and a half hours tracheotomy and débridement of his two wounds were done. By the next morning the patient's condition had significantly improved. Clinical symptoms, including tetanospasm, persisted but were relatively mild and at no time thereafter were embarrassing to the vital functions. The dose of cortisone was progressively decreased as the patient's condition improved. He was clinically free of any evidence of tetanus when dismissed from the hospital on the twenty-third day of his disease. A small dose (25 mg. per day) of cortisone was continued for another week at his home.

To our knowledge, this is the first patient to receive cortisone in the treatment of tetanus. Although significant improvement followed administration of the preparation, further experience will be necessary fully to evaluate it as an effective adjunct in the treatment of tetanus.

Morbidity was not affected by the use of cortisone. Definite undesired side effects were not noted. Wound healing was not observed to be delayed. Serum reactions did not occur. 10 references.—*Author's abstract.*

212. *Use of Quinidine in Treatment of Chronic Auricular Fibrillation.* ERNEST N. YOUNT, MARVIN ROSENBLUM, AND ROBERT L. MCMILLAN, Winston-Salem, N. C. Arch. Int. Med. *89*:63-69, January 1952.

Of 155 patients with chronic auricular fibrillation who were given quinidine, 50 per cent had arteriosclerotic heart disease, 30 per cent rheumatic heart disease, and the remainder thyrotoxicosis or "miscellaneous conditions." All these patients were treated in the hospital and electrocardiograms were made before and during quinidine therapy. Quinidine sulfate was given by mouth every four hours day and night, beginning as a rule with a dose of 2.2 Gm., and increasing each dose by 0.1 or 0.2 Gm. at the end of each twenty-four or forty-eight hour period. Recently the 4 a. m. dose has been given in an enteric coated tablet with the midnight dose, so as not to interrupt the patient's sleep. Sinus rhythm was restored in 119, or 76 per cent of the 155 patients, and in 86 per cent of those who were given an adequate therapeutic schedule. At the time of the reversal of the rhythm, the average dose every four hours was 0.42 Gm. and the mean plasma content of quinidine in the patients in whom it was determined, was 9.1 mg. per liter. Good results were obtained in 19 of 23 patients in the oldest age group (seventy to eighty-six years), and these results were obtained with smaller doses than were necessary in the other groups; and results in patients in whom the auricular fibrillation had persisted more than two years, were as good

as in those whose arrhythmia had been present less than six months. The only underlying disease that affected the response to quinidine unfavorably was thyrotoxicosis. After normal rhythm was restored, the dosage employed at that time was continued for twenty-four to forty-eight hours; if the normal rhythm persisted the same individual dose was given every six, instead of every four, hours; later, if there was no recurrence of the arrhythmia, this dose was still further reduced.

Most of the patients treated were returned to the care of their own physicians, and adequate follow-up data have not been obtained. Of 41 patients followed up through out-patient clinic of the hospital, only 6 have shown a recurrence of auricular fibrillation; in these patients, the average maintenance dose on the six-hour schedule has been approximately one-half of the dose employed at the time of reversion to normal rhythm.

Gastrointestinal disturbances were observed in 30 per cent of the patients, but were of mild type; symptoms of central nervous system or labyrinthine origin occurred in 15 per cent, but were not sufficiently severe to make it necessary to discontinue therapy. There was no case of precipitant fall in blood pressure, and no case of hypersensitivity to the drug, as evidenced by collapse and cardiorespiratory failure after the first administration of the drug. There was only 1 death in the series occurring suddenly in a patient with severe congestive heart failure on the sixth day of treatment. Twenty-three patients who had shown evidence of an embolus before quinidine treatment showed no further emboli after normal rhythm was restored by quinidine; only 2 patients developed embolic symptoms during treatment. 13 references, 4 tables, 1 figure.

213. *Roentgen Aspects of Pulmonary Arteriovenous Fistula.* WILLIAM B. SEAMAN AND ALFRED GOLDMAN, St. Louis, Mo. Arch. Int. Med. *89*:70-81, January 1952.

Roentgenographic studies of 8 cases of pulmonary arteriovenous fistulae are reported; clinical studies of 4 of these cases have been previously reported. The ages of these patients varied from twenty-two to seventy-nine years; the oldest patient was in general good health and was referred for study because roentgenological examination for virus pneumonia had shown a pulmonary mass, the nature of which was not determined. With the usual chest roentgenogram, the diagnosis of pulmonary arteriovenous fistula can be made if there are tortuous and band-like opacities, communicating with the hilum and also with a lobulated soft-tissue tumor in the parenchyma. If the fistulae are small, the appearance of the opacities may not be characteristic and may resemble other pulmonary lesions. In establishing the diagnosis, it is most important to demonstrate the relation of the mass to the blood vessels. In the fluoroscopic study, the Muller test may be used; it increases the negative intrathoracic pressure, which results in a distention of the fistula with blood. This test is not always positive and was not used in all the 8 cases reported, but was positive in 2 of them. The authors are of the opinion that this procedure should be used when pulmonary arteriovenous fistula is suspected but not definitely demonstrated by the usual roentgenological methods. In some cases the pulsatile nature of the mass may be demonstrated both by fluoroscopy and by roentgen kymography; pulsations were

demonstrated by both methods in 2 of the author's cases. Laminography is a valuable method of demonstrating the vascular relations of the pulmonary shadow, and employed with the usual chest roentgenograms, is usually sufficient to establish the diagnosis of pulmonary arteriovenous fistula. Angiography has been used in some cases, but involves danger of sudden death, especially in patients with hypertension or cardiac failure. The authors are of the opinion that it should be employed if surgical treatment is contemplated, especially as it is of value in demonstrating multiple lesions not otherwise discovered. 20 references. 1 table. 10 figures.

214. *Use of Corticotropin and Cortisone in Acute Homologous Serum Hepatitis.* HAROLD RIFKIN, LEON J. MARKS, DAVID J. HAMMERMAN, MORTIMER J. BLUMENTHAL, ALTER WEISS, AND BERTHOLD WEINGARTEN, New York, N. Y. Arch. Int. Med. *89*:32-40, January 1952.

In 4 cases of acute homologous serum hepatitis, corticotropin or cortisone was employed, when the patients failed to improve although taking a fairly satisfactory diet supplemented by vitamins and liver extract given parenterally. In all these cases the administration of corticotropin or cortisone resulted in prompt clinical improvement and increased appetite. In 2 of the 4 cases a relapse occurred after the steroid treatment was discontinued, but this also responded promptly to another course of treatment. Although corticotropin and cortisone undoubtedly halt the rapid progress of acute homologous serum hepatitis, they do not necessarily alter the basic mechanism of the disease. In 1 of the cases reported the condition had advanced to a typical phase of chronic hepatitis. The exact mode of action of cortisone and corticotropin in acute hepatitis has not been determined. 13 references. 3 figures.

215. *Intravascular Distribution of Na Injected Intravenously in Man.* LOUIS BAKAY, BERTRAM SELVERSTONE, AND WILLIAM H. SWEET, Boston, Mass. J. Lab. & Clin. Med. *83*:893-903, December 1951.

Following the intravenous injection of a few cc. of a solution of $Na^{24}Cl$, the sodium is completely mixed in the major arteries to limbs and head in man, in less than a minute.

Gross variations occur in time for venous concentrations to attain those in the arterial blood. The superficial veins of the feet and legs lag markedly behind those of the upper limbs unless the individual is vigorously active. Sluggish circulation, accompanied by the flow of unlabeled sodium from the extravascular fluid and/or blood pooled in stagnant veins, markedly delays mixing. This may be associated either with a motionless state, multiple local thromboses, or vasoconstriction.

When rates of transcapillary exchange of electrolytes are to be studied, many early arterial determinations are desirable, since one can be certain of complete mixing before the first minute only in these vessels, and the more rapid of the various rates of exchange are so fast that they may be missed by analyses of later data. We suggest that three, rather than two, rates of exchange of Na^{24} per minute may more nearly describe the processes occurring normally. Such rates in a motionless stuporous man

were 55 per cent, 9 per cent, and 2 per cent, and in a powerfully moving person were 150 per cent, 10 per cent and 0.2 per cent. 6 references. 6 figures.—*Author's abstract.*

216. *Oral Use of Cation-Exchange Resins in Treatment of Edema.* KENDALL EMERSON, JR., STANLEY S. KAHN, JOHN W. VESTER AND K. DEXTER NELSON, Boston, Mass. Arch Int. Med. *88*:605-17, November 1951.

The effect of two types of cation-exchange resins—Permutit Z, a sulfonated polystyrene-type resin, and Amberlite XE-96, a crosslinked, polysacrylic (polycarboxylic) resin—upon the fecal excretion of cations, has been studied quantitatively in five patients. When 40 to 60 Gm. of resin were administered per day, fecal sodium varied from 15.6 to 36.1 m.Eq. and fecal potassium increased by 12 to 96 m.Eq. per day. There was no significant change in the fecal excretion of calcium and magnesium. Increase in urinary ammonia excretion occurs to offset the loss of base in the feces. In one patient with severe renal damage, the kidneys were unable to form ammonia, and acidosis resulted from resin administration. Six patients with various forms of edema were treated for periods ranging from six months to two years. The polycarboxylic resin, administered in the ammonia and potassium cycle, contained 5.7 per cent potassium by weight, and was approximately sufficient to replace the amount removed in the intestinal tract. In all of these patients the edema was partially or completely controlled without need for other diuretics. In one patient treated for two years there was a reduction in total body potassium of about 500 m.Eq. with a similar increase in total body sodium. It would appear wise, therefore, to administer supplementary potassium in prolonged therapy. 11 references. 4 figures. 4 tables.—*Author's abstract.*

217. *Importance of Life Stress in Course and Management of Diabetes Mellitus.* LAWRENCE E. HINKLE, JR. AND STEWART WOLFE, New York, N. Y. J.A.M.A. *148*:513-20, Feb. 16, 1952.

Experimental evidence indicates that stressful life situations may lead to important metabolic changes in persons with diabetes mellitus, and that these may be accompanied by emotional and behavioral changes. Ketonemia and an increased excretion of water, glucose, and chlorides were observed, as well as alterations in fasting blood sugar, which might lead to either hyperglycemia or hypoglycemia.

Study of the life histories and daily experiences of persons with diabetes indicates that many of the apparently spontaneous fluctuations in the syndrome are the results of life stress. The similarities in the life histories of these diabetic persons suggests that developmental, cultural, and psychologic factors may have an important influence on the onset and course of the disease. Their behavior under stress, their attitudes toward food, and their feelings toward their parents are often so similar as to suggest that these psychologic manifestations might be considered as symptoms of the total disease process.

Treatment directed at alteration of the behavior and attitudes of the patient and

his relation to his environment is helpful in abolishing otherwise uncontrollable fluctuations in the course of labile diabetes and in preventing recurrent episodes of ketosis requiring hospitalization. In all cases of diabetes an understanding of the patient and his life situation is necessary in order to understand the course of the disease, the limitations of therapy, and the goal which may be attained. 9 references. 13 figures.—*Author's abstract.*

218. *Endemic Infectious Hepatitis in an Infants' Orphanage: Epidemiologic Studies in Student Nurses.* RICHARD B. CAPPS AND ALFRED M. BENNETT, Chicago, Ill. and Joseph Stokes, Jr., Philadelphia, Pa. Arch. Int. Med. *89*:6-23, January 1952.

In a study of the epidemiology of infectious hepatitis among student nurses in an orphanage, caring for children less than three years old, it was demonstrated that some of the children had infectious hepatitis and that these children infected the student nurses by person to person contact. The presence of infectious hepatitis in 26 children was established by clinical and laboratory studies and by the infection of volunteers with material from the feces of 2 children with the disease. All but one of these children, however, were free from jaundice or hyperbilirubinemia, thus indicating the importance of unrecognized, nonjaundiced cases in the spread of infectious hepatitis. For several months during the period of this study, gamma globulin was given to student nurses on admission to training; during this period only 1 case of infectious hepatitis developed among the student nurses, and in this case gamma globulin was given too late. The establishment of aseptic nursing technic throughout the orphanage prevented further spread of infection and terminated the outbreak of the disease among the nurses. 39 references. 6 tables. 8 figures.

pediatrics

219. *Infant Feeding With and Without Added Carbohydrate.* LLOYD E. HARRIS, Rochester, Minn. Am. J. Dis. Child. *82*:677-84, December 1951.

This paper presents comparative experiences in the use of formulas with and without added carbohydrate for infant feeding. Each experimental group numbered 30 to 90 infants, and did not include those prematurely born. All were followed for at least 6 months.

Average gains in weight were essentially the same for infants taking formulas without added carbohydrate as for those taking added carbohydrate. The intakes, as reported by the mothers, were essentially the same for both types of formula. Cereal was offered with equal frequency in both types of feeding. There were fewer infants having firm to hard stools among those receiving a formula without added carbohydrate than among those taking added carbohydrate. The incidence of "colic" was perhaps somewhat less in those receiving no added carbohydrate. 5 references. 5 tables. 2 figures.

220. *Paralyses Following Immunising Injections. Measures Calculated To Diminish the Risk.* G. BOUSFIELD. Lancet *1*:1028-32, May 12, 1951.

In England and Wales the reported incidence of poliomyelitis in the period 1946-1949 was much less in the 1st year of life than in the next few years of childhood. The period of greatest incidence was between the second and fifth years. In children under 1 year the disease in recognizable form was relatively infrequent under the age of 6 months. In view of this it is suggested that the risk of post-injection paralysis is probably less in the first 6 months of life than in the next few years, and that immunization against diphtheria should be undertaken as early as possible in life, for example at the age of 2-3 months. Evidence is offered that infants can be immunized successfully at this age and that the immunity holds good some 18 months to 2 years later in the great proportion of cases. With the subcutaneous method of administration no paralytic sequelae have been observed in infants up to 5 months of age.

221. *Accidental Poisoning in Children.* L. T. CHUN, Honolulu. Hawaii Med. *11*:83-87, Nov.-Dec., 1951.

Over a period of 5 years, 221 cases of accidental poisoning were hospitalized. There were 3 deaths due to one each of the following: kerosene, water color paint, and oil of eucalyptus. There were twice as many boys as girls. The age of greatest frequency was 2 years, followed by the age groups of 1½ years, 1 year, 3 years, and 2½ years.

Fifty-nine different poisons were encountered. The most frequent was kerosene (69 cases). Other common ones were arsenic compounds, oil of eucalyptus, phenolphthalein, barbiturates, pine oil, salicylates, and camphorated oil.

The most common general treatment was gastric lavage. One hundred sixty seven clients were so treated. In most instances, the exact amount of ingested poison was unknown. The time interval before the patient was seen was usually one-half to one hour.

Kerosene poisoning is discussed in detail. The most frequent complications are fever, cough, pneumonia, vomiting and lethargy. No conclusions could be drawn as to the frequency of complications between those who were lavaged and those who were not. 1 table.

222. *A Report on the Hearing Survey in the Public Schools of Pennsylvania.* JAMES E. LANDIS, Reading, Pa. Pennsylvania M. J. 55:233-35, March 1952.

A state program has been inaugurated in Pennsylvania for the testing and disposition of deafened school children. In this program the multi-audiometric testing has been discontinued wherever possible for the following reasons: the test often loses its validity because the children, thinking it is some sort of school examination, are apt to cheat or copy from each other; this method fails to detect early high tone deafness; the diagnostic curves show a lesser degree of accuracy than those of other testing

methods: operation of the test usually disrupts the entire class: there are too many repeats and referrals. Puretone audiometry is recommended because: it has greater ease of operation: one can command individual attention: the individual curves show a greater degree of accuracy: and the trained technician, usually a nurse, can examine an entire class with much greater speed than with other methods. By sweep testing, 20 to 30 children can be tested in both ears within an hour. Those children who show more than 15 decibels loss are re-examined afterwards more slowly. School children are tested in the first, third, fifth, seventh, ninth, and eleventh grades. Those with a 20 decibels loss in two or more tones in one or both ears are referred to a recognized otologist for diagnosis and recommendations for treatment.

In a group of 1,158,642 children outside of Philadelphia and Pittsburgh who were thus tested, 43,932 or 3.8 per cent had some hearing loss. The deafness in those children who were examined later by otologists was found to be of the conductive type in 69 per cent, perceptive in 10 per cent, mixed in 8 per cent, otosclerotic in 11 per cent, and miscellaneous in 2 per cent. Infected tonsils or adenoids or both were the most common causes.

These children have been divided into three types. The *deaf* child is one with no usable threshold of hearing and in whom no threshold can be developed from any practical standpoint. Such a case must be institutionalized at present. The cost of each case amounts to $1,800 per year. There are over one thousand children in schools for the deaf in Pennsylvania, supported by the Department of Public Instruction. The *deafened* child never has had normal hearing but does have some usable threshold which, with the proper training, can be made into an effective means of auditory communication. Such a child should be kept out of schools for the deaf since he will benefit to a greater extent by a combined parent-child program developed with the assistance of proper school handling. The *hard of hearing* child is one who has had normal hearing in the past but has lost his hearing as a result of some pathologic change. He, too, must be kept out of schools for the deaf, and his training effected at home through a program involving cooperation between the parents and teacher.

Such a hearing conservation program pays tangible dividends which are apparent in happier social relationships, more gainful employment improved economic status, and satisfactory psychologic adjustments. 3 tables.

223. *Transmission of Poliomyelitis Virus, Analysis of Differing Interpretations and Concepts, Practical Implications.* ALBERT B. SABIN, Cincinnati, Ohio. Chicago M. Soc. Bull. *54*:163-71, Sept. 15, 1951.

Available knowledge justifies the conclusion that human feces derived from patients and healthy carriers is the most significant source of virus in nature. The virus which is occasionally present in the throat of patients and healthy carriers apparently does not *ordinarily* reach the outer environment in significant amounts by droplets from the mouth or nose.

The period of communicability cannot at present be said to be limited to a few days before and a few days after onset of illness. It should rather be regarded as

potential during the period that virus is generally eliminated in the feces. The period of communicability may be greatest during the few days before and the week after onset, because the amount of virus eliminated in the feces during that period may be greatest, but there is no specific quantitative information on this point. One may use as guide the fact that approximately 50 per cent of patients still have demonstrable virus in their stools 3 to 4 weeks after onset. It is not justifiable to stress one method whereby stoolborne virus may be transmitted and to minimize others, because the relative importance of any one method can vary with the circumstances.

Excepting artificial conditions, entry of poliomyelitis virus by way of the mouth can be justifiably regarded as the usual mode of infection. Accordingly, contaminated food and drink are as important as contaminated fingers in introducing the virus into the body.

Under certain conditions in both urban and rural communities, filth, flies, as well as human beings can be carriers of poliomyelitis virus. The incidence of infection naturally varies in both. In some limited outbreaks, the familial associates of recognized cases are most important as carriers, while in large metropolitan, urban epidemics, the cases and carriers are widely scattered throughout the city. By the time the existence of an epidemic is recognized in a large city, there are usually already so many healthy human carriers that neither complete isolation of patients and their associates nor the destruction of the filth-fly carriers can be expected to stop an epidemic. This is the real basis for the general agreement that there is no justification for initiating emergency insect control measures in the hope of stopping a poliomyelitis epidemic. However, individual measures designed to combat filth flies and to minimize contamination of food by flies in markets or homes should receive the same encouragement as the observance of other hygienic measures which are designed to diminish the chances of infection for the individual. Many methods of transmission are involved in a large outbreak of poliomyelitis. No single measure can be relied upon for crucial effectiveness.

Subclinical immunization appears to occur during nonepidemic years as well as during epidemics. There is reason to believe that strains of greater virulence are in circulation in a community during an epidemic period. Even though the existence of large numbers of unrecognizable healthy human carriers imposes an insuperable obstacle in the control of a large epidemic, it is sound practice to maintain isolation procedures because of the known potential infectiousness of recognizable and suspected cases and their intimate associates.

Since there is no evidence for the transmission of poliomyelitis by droplet nuclei, the following measures which are sometimes advocated during poliomyelitis epidemics are not warranted:

a.) Avoidance of crowds, large public gatherings or sports events.

b.) Exclusion of children under 16 from movies, churches or schools.

c.) Exclusion of poliomyelitis patients and suspects from general hospital wards.

On the other hand, it appears reasonable during *epidemic periods for individuals* to take the following simple steps to diminish the risks of acquiring infection:

a.) Keep fingers out of mouth and wash hands before eating.

b.) Keep flies away from all food, and thoroughly wash that which is consumed uncooked, e.g., vegetables, fruit, etc.

c.) Keep children under 16 out of crowded public wading and swimming pools.

d.) Avoid *intimate* association (shaking hands, etc.) with members of a family in which a case of poliomyelitis has occurred within 3 weeks, even though the patient has been removed to a hospital. 34 references.

224. *Second Attacks of Paralytic Poliomyelitis in Human Beings in Relation to Immunity, Virus Types and Virulence, with a Report of Two Cases, and Four Other Individuals in Baltimore, 1944, Infected with Virus of the Leon Type.* D. BODIAN, Baltimore, Md. Am. J. Hyg. 54:174-90, Sept. 1951.

The Leon type of virus was isolated from the stools of two boys during the acute stage of second attacks of paralytic poliomyelitis during the 1944 outbreak in Baltimore. Four additional strains of the Leon type were isolated from two fatal bulbar cases, a paralytic case, and an asymptomatic case, respectively. The six Leon-like strains were low in virulence for monkeys, one exceptionally so. From the same outbreak, three strains of the Brunhilde type were also isolated from the throat swabs of young children with asymptomatic or abortive infections and from a paralytic case, so that more than one virus type was prevalent. Moreover, strains of both the Brunhilde and Leon types were isolated from children in the same playground community.

The first patient experiencing a second attack at the age of 15 years had antibody against the Leon virus and against virus from his own stools at the time of the second attack. The antibody titer rose ten-fold 3 months later against both viruses, and receded after 5 years to the level observed in the acute phase of the second attack. Serum antibody against the Brunhilde and Lansing types was not present at any time during this period of 5 years. No evidence regarding the virus producing his first paralytic attack at the age of 9 months was, therefore, obtained.

The second patient had a first attack at the age of 12 years. During the second attack his serum contained traces of Lansing antibody, no Leon antibody, and a high level of antibody against Brunhilde virus (1 in 100), which appeared to be undiminished after 5 years. At this time, his serum still contained minimal detectable amounts of Lansing antibody, but had acquired a high titer of Leon antibody (1 in 100). The findings suggest that the first illness was caused by a virus of the Leon type.

In view of the good antibody response of both patients, and other evidence presented, second attacks of paralytic poliomyelitis in human beings may be regarded as being due to reinfection with virus of an antigenic type different from that producing the first attack. 23 references.

obstetrics

225. *The Test of Labor—An Evaluation of Its Present Worth.* ARTHUR B. HUNT, Rochester, Minn. J. A. M. A. *147*:999-1004, Nov. 10, 1951.

From this study certain points need emphasis, certain impressions seem important, and certain conclusions can be drawn.

The factors that have made for recent reduction in maternal mortality have provided much more latitude in applying the test of labor than prior to about 1937. This change should reduce the incidence, and I believe that it has, of very difficult, traumatizing forceps deliveries.

With more than 50 per cent prospects for successful pelvic delivery, with no appreciable maternal mortality, and with a fetal loss no greater than 2.3 per cent, a reasonable trial or test of labor, as the case may be, is thoroughly justified.

The triad of fetal size, uterine inertia and contracted pelvis is the chief factor in the success or failure of the test of labor and is of importance in the order named. The effect of the contracted pelvis on the test of labor has been exaggerated at the expense of fetal size and uterine inertia. Of the adjunct factors, fetal malpresentation is of special significance in the success or failure of the test of labor.

To date there is no better way to justify an initial cesarean section than a failed test of labor.

Successful tests of labor mean that about three fourths of the patients in future pregnancies will have pelvic deliveries but does not guarantee freedom from future dystocia, since the remaining fourth, as indicated by our group, will have some difficulty in subsequent labor. Of those who had difficult labor subsequently, about half did not have great difficulty, but the other half had severe dystocia and usually failed the test of labor, and cesarean section was necessary.

The selection and conduct of the test of labor require a high degree of individualization in each case and, therefore, a fine quality of both the art and science of obstetrics. The test of labor is also the test of the obstetrician. It tests his powers of observation, vigilance, judgment, obstetric conscience, and technical skill. By the exercise of these powers, good results usually can be obtained. 10 tables.

This is an interesting paper, but as usual, does not define just what is a test of labor. One statement of the author does not seem to be in accord with the facts. "There is no better way to justify an initial cesarean section than a failed test of labor." It is the general experience that such patients are fatigued, the baby may have suffered from pressure trauma and the moment of election has been lost. Cesarean section after failed labor constitutes, really, an emergency operation and is often more complicated in its performance and results than a purely elective operation.—E. A. S.

226. *Obstetrics in General Practice.* CLYDE L. RANDALL AND RICHARD W. BAETZ, Buffalo, N. Y. Pennsylvania M. J. *45*:129-38, December 1951.

We believe the majority of physicians in general practice are qualified to do the best possible type of obstetrics. This does not mean that we feel most practi-

tioners are capable of doing the best procedure in every instance, but the complications indicating the services of a specialist should appear in less than 10 per cent of maternity patients.

In the late weeks of pregnancy and particularly in the early phases of labor, if home delivery is being considered, a decision must be made as to which cases can be managed safely at home and what conditions indicate hospitalization. Patients with complicating disease, with a history of excessive bleeding at the time of a previous delivery, with the actual occurrence of antepartum bleeding, with signs of toxemia or the development of dystocia, cannot be safely managed without hospitalization.

We are indebted to the proponents of "natural" childbirth for emphasizing the importance of maternal relaxation during labor. Sedation is indicated as early in labor as apprehension or tension begin to interfere with the mother's ability to relax between contractions.

At the time of actual delivery, the choice of anesthetic agent is important and we consider those agents which quickly relax the perineal musculature most desirable. Local infiltration of novocain by regional block or a low spinal injection are ideal and both assure satisfactory anesthesia for completion of the third stage and repair of an episiotomy. Either can be given to the patient shortly after ingestion of a full meal, and are not contraindicated with an upper respiratory infection.

If inhalation anesthesia is to be used, we feel it should be withheld until conditions are right for completion of the delivery. At this time anesthesia, to a point of perineal relaxation, should be accomplished as quickly as safe induction allows, episiotomy performed, and the baby promptly delivered by low forceps before enough anesthesia reaches the baby to depress fetal respiration.

Most obstetricians of experience, reading recent condemnations of the routine employment of analgesia, episiotomy, and low forceps delivery, question the basis upon which criticisms are offered. We realize that some physicians believe spontaneous delivery in a patient who is unafraid a less traumatic affair than we have witnessed when women have been psychologically unprepared for labor. Eventually the record of a large series of cases may provide evidence that mothers psychologically and physically prepared for labor and "natural childbirth" can, without analgesia, anesthesia, or episiotomy, deliver spontaneously with the loss of fewer babies than are now lost during a comparable number of cases managed by DeLee's "prophylactic" regimen.

We believe that the best possible management of pregnancy and parturition, in more than 90 per cent of cases, involves only those services that the general practitioner is fully qualified to render (i.e., personal attention and intelligent advice during the prenatal period, moral support and the necessary sedation for relaxation during the first stage of labor, and, finally, delivery by low forceps with episiotomy under anesthesia as soon as the vertex reaches the perineum). The current emphasis of so-called natural childbirth is reassuring many prospective parents of the capability of their family doctor. Although the practitioner must occasionally anticipate difficulty and promptly advise consultation for operative delivery, he can conscien-

tiously and wisely insist on conservative management for almost all deliveries and be practicing good up-to-date obstetrics. 2 references. 5 figures.

227. *Tubal Pregnancy Complicating Tuberculous Salpingitis.* ROBERT W. KISNER, ARTHUR T. HERTIG AND JOHN ROCK, Boston, Mass. Am. J. Obst. & Gynec. *62*:1157-59, November 1951.

Extra-uterine pregnancy in the presence of tuberculous salpingitis is an extremely uncommon pathologic condition; a total of 41 cases have previously been reported. In the 54 years the Pathologic Laboratory of the Free Hospital for Women has filed microscopic reports, there have been 197 cases of tuberculous salpingitis and 313 cases of tubal pregnancy. The following case is the first in this laboratory in which these two conditions have coexisted.

A 22 year old, white, para 0, was seen in the clinic with a two year period of sterility. Past history revealed pleurisy of unknown etiology at 14 years of age. Endometrial biopsy revealed normal 22 day secretory endometrium. Two years later the patient was again seen because of irregular vaginal bleeding of six weeks' duration. A tender, firm resistance was palpable on the right side. At laparotomy the right tube was distended in its outer third and an old blood clot blocked the fimbriated end. A resection of the tube and ovary was carried out. The pathologic report was: tubal pregnancy, with blighted ovum; acute and chronic salpingitis; tuberculous endometritis (concomitant dilatation and curettage having been done). Further sections of the tube were then cut which revealed tuberculous salpingitis and acid-fast stains on the tubal material were positive. The patient was readmitted six months later and a complete hysterectomy and bilateral salpingectomy was performed, with the ovaries preserved. An uneventful recovery ensued.

It is the impression of the authors that tuberculous salpingitis-ectopic pregnancy is rare because: (1) the disease process is usually bilateral and sterility is a common finding in this group; (2) the necrotic mucosa provides unfit ground for nidation of a "ripe" egg; (3) insufficient microscopic examination or insufficient blocks may not reveal the typical lesions. In this regard, uterine curettage may be of aid, since the lesion, as in this case, may be detected in the curettings and then multiple sections of the tube prepared; (4) the ovum, possibly trophoblastically inefficient, may be unable to implant; and (5) the reported high incidence of tubal occlusion prevents fertilization. 18 references.—*Author's abstract.*

228. *Jaundice During Pregnancy.* MOGENS INGERSLV AND GUNNAR TEILUM, Copenhagen, Denmark. Acta obst. et gynec. Scandinav. *31*:74-89, fasc. 1, 1951.

Ninety-one cases of jaundice during pregnancy were seen in an 8 year period. Twenty-five had no other symptoms, and most of the cases were very mild. In nearly all, jaundice developed after the twenty-third week; it lasted just over five weeks when it cleared up before delivery and scarcely four weeks when it extended

into the puerperium. Its average duration after delivery was 11 days, regardless of its duration beforehand. Liver function tests were usually negative. Out of 6 cases of liver biopsy, 1 revealed typical hepatitis; 2, mild but unmistakable hepatitis; and 3, normal liver tissue.

It is thought that at least a large proportion of the 91 cases had had hepatitis. The incidence of hepatitis in the population corresponds more or less to the incidence of jaundice in pregnancy, and the same seasonal variations were observed. Pregnant women appear to be liable to hepatitis in the second half of pregnancy, but it is only mild; its further course depends upon whether the pregnancy continues.

Syphilis was very common among pregnant women with jaundice, presumably because they are exposed to the risk of inoculation hepatitis.

The maternal prognosis was good; only one mother died from acute yellow atrophy. The fetal mortality was 15 per cent, mainly because the mothers tend to abort, or to go into premature labor.

Treatment should be conservative in principle until it is thought that the fetal weight exceeds 2500 Gm. At that stage, labor should be induced, except in very mild cases. Induction of labor is recommended regardless of the fetal weight when jaundice develops rapidly, and in very severe cases, particularly when the general nutrition of the mother is poor.

The transmission of hepatitis by inoculation can be avoided by boiling or dry-sterilizing cannulae and syringes. Doctors and midwives should protect themselves by the use of gloves when attending icteric women in labor. 13 references. 2 figures. 5 tables.

229. *Multiple Simultaneous Unilateral Tubal Pregnancy. A Case Report.* ROBERT KAPSINOW, Lafayette, La. New Orleans M. & S. J. *104*:232-34, December 1951.

A case report of an unusual complication of pregnancy deals with a twin pregnancy in one tube at about 3 months. No previous record has been found in the literature of a similar case. The only other reference cites a case at six weeks. In spite of the enormous amount of intra-abdominal bleeding that took place, the patient recovered in such a rapid manner following surgery that she was able to return home on the sixth day. The history of a missed period should always suggest the possibility of ectopic pregnancy. 1 reference.—*Author's abstract.*

230. *Diabetes Mellitus and Pregnancy.* H. I. CRAMER, Montreal, Quebec, Canad. M. A. J. *65*:328-33, October 1951.

A series of 84 pregnancies in 73 diabetics is presented and analyzed; the maternal survival was 100 per cent and the fetal mortality was 30 per cent.

Multiparae showed a much higher fetal mortality than primiparae. The age of the mother showed no effect upon the fetal mortality rate. Long duration of the diabetes increased the fetal mortality. Juvenile diabetics showed a very high fetal mortality rate. The older the mother at the onset of her diabetes the lower the fetal

mortality. Severe diabetics showed a higher mortality rate than mild diabetics, and all our cases of diabetic acidosis terminated in the death of the fetus. There was no relationship between signs of toxemia of pregnancy and fetal death rate, nor any relationship between the level of the serum prolan and fetal death rate. A series of multiparae in whom one or more previous pregnancies had resulted in fetal death showed no higher fetal death rate than other multiparae.

Cases submitted to cesarean section showed a very low fetal mortality (8 per cent). The average fetus born at term weighed 3,850 Gm.; seventeen weighed over 4,000 Gm. There was no difference in the average weights of live or dead fetuses born at the same period of the pregnancy. Poor or no diabetic treatment resulted in a somewhat greater average fetal weight, and toxemia of pregnancy also caused a small increase in the average weight. A series of 16 fetuses, weighing over 4,000 Gm. and born 2 to 15 years before the development of the diabetes in the mother, is also presented. 17 references, 7 tables.

231. *On the Toxaemias of Late Pregnancy.* PAAVO VARA AND KAISA VEHNIAINEN, Helsingfors, Finland. Acta obst. et gynec. Scandinav. *31*, Suppl. 4:5-84, 1951.

A series of cases of toxemias of late pregnancy has been collected from the Second Women's Clinic in Helsinki over a period of five years (1945-1949). In these patients the clinical development of the condition was followed, and at the same time attention was given to the pathophysiologic phenomena associated with this. The material comprises 1,602 toxemia patients, 581 being albuminuria and 474 nephropathy cases, which together form the mild toxemia group. The group of severe toxemias consists of 269 preeclampsia and 52 eclampsia patients. In addition, in this investigation 164 patients are included who have been diagnosed as having hypertension, since in these patients the blood pressure after delivery has remained raised either permanently or over a long period. Proteinuria has been of mild degree and disappeared rapidly after delivery. In some patients, in addition to increased blood pressure, marked proteinuria occurring before delivery has disappeared slowly after delivery or remained permanent. These have been included in the nephritis group, consisting of 62 patients. This division most closely resembles that of the American Committee on Maternal Welfare.

The number of patients with toxemias of late pregnancy has increased in our clinic year by year. In the majority, however, toxemia has been of mild grade, as proved by the fact that the frequency of eclampsia has remained practically constant during the last three years.

On comparing the duration of labor in toxemia patients with the values observed in healthy women with a normal pelvis, it would seem as if it were, as a rule, prolonged. In the albuminuria group this difference is statistically significant both in young primiparae and in multiparae; in elderly primiparae the difference is probable. In the nephropathy group, the prolongation of labor is statistically significant only in young primiparae; in the others the difference is "possible." In both the eclampsia and preeclampsia groups, no statistical difference is obtained. The pro-

longation of labor is, however, affected by the fact that the cases with a narrow pelvis have not been separated from the material.

The time from the artificial rupture of the membranes to the beginning of expulsive labor pains in toxemia patients in the different severity groups is, as a rule, shorter than the time between spontaneous rupture of the membranes and the expulsion pains, indicating that the artificial rupture of the membranes definitely shortens the duration of labor in toxemia patients. The incidence of spontaneous rupture of the membranes in the different stages of labor indicates the usual course of delivery in toxemia patients also.

In the albuminuria and nephropathy groups, the incidence of forceps delivery varies within lower limits than the corresponding frequency found in healthy primiparae with a normal pelvis; the frequency of cesarean section, on the other hand, is higher in both. In these groups the clinical picture, however, is still so mild that it cannot be considered to have much bearing on the incidence of operation; the indications for operation have been due to other reasons.

In preeclampsia patients the clinical picture is already more severe and the incidence of operation is correspondingly higher. The highest incidences in both the use of forceps and cesarean section occur in eclampsia patients. In patients of the hypertension group, the frequencies of both forceps and cesarean section occur in eclampsia patients. In patients of the hypertension group, the frequencies of both forceps delivery and cesarean section vary at a lower level than in the albuminuria group. This can be explained by the fact that in many patients of this group the clinical picture has been fairly mild. In the patients of the nephritis group the frequency of cesarean section must nearly corresponds to that found in the eclampsia group, the frequency of forceps delivery being fairly low. In elderly primiparae the frequency of operation has, a a rule, been higher than in young primiparae, and in primiparae usually higher than in multiparae.

The material mortality varied from 0.4 to 1.2 per cent, the total mortality being 0.81 per cent.

The frequency of premature deliveries was highest in eclampsia and nephritis patients, the preeclampsia group occupying the next place. The mortality of premature infants was 42.5 per cent and that of full term 1.56 per cent.

In this treatment, increased attention has also been devoted to the prevention and treatment of shock, especially taking into consideration the significance of hypoproteinaemia and decreased colloid osmotic pressure in the mechanism of shock production.

With this in view, a 10 per cent salt free dextran solution (Macrodex) has been used, which has, up to now, given good results, the amount of urine increasing and the edema disappearing. 129 references. 25 tables.

psychiatry

232. *Medical Responsibility for Juvenile Delinquency.* NATHAN BLACKMAN, St. Louis, Mo. Postgrad. Med. *10*:499-503, December 1951.

The author reviews the more salient factors contributing to our failure in handling delinquency. He describes the need to modify the McNaughton Laws in light of accrued knowledge about motivation and emotionality of growing up. The discrepancy between the legal attitude which concentrates on administering punishment for an offense and the medical view which considers the individual and his reasons for committing the offense are described.

It is pointed out that most delinquencies are listed as crimes against society, whereas in the distant past they were traditionally directed against the father. The abdication of the father as the frustrating person bearing the brunt of aggressiveness from juveniles and the transfer of this hostility to "society" is a phenomenon of modern life.

The juvenile delinquent cannot repress aggressiveness and has a lack of genuine affection for either parent. Sometimes the child needs to create irritation and anger in order to justify his tendency to project unto others his difficulties of growing up. The parent, harboring subconscious hostility toward the child, reacts with anger toward the child's misbehavior, thus justifying his own inability to love the child. In tracing the need of belonging in the growing child, his need for acceptance and his quest for identification with a meaningful adult are described.

The child becomes aggressive or antisocial as a need to atone, to assuage a deep seated disquietude about his presence in this world. He counters the deep seated fear of parental anger with another fear of something that he has himself created, manipulated, and dared. Thus the author ascribes to delinquency an expression of insecurity by the child due to a grim awareness of being isolated, being unable to trust or depend on his immediate, close to him, adult. 14 references.—*Author's abstract.*

233. *Long-Term Study of Combat Area Schizophrenic Reactions, Preliminary Report.* HERBERT S. RIPLEY, Seattle, Wash., AND STEWART WOLF, New York, N. Y. Am. J. Psychiat. *108*:409-16, December 1951.

One hundred patients with schizophrenia or schizophrenic-like reactions, occurring in a combat area, have been investigated. Follow-up data over a period of five to eight years, after the initial hospitalization, were obtained through records, questionnaires, and personal interviews.

There was a high incidence of psychopathologic symptoms prior to the illness developing overseas. The most common precipitating factors appeared to be traumatic incidents in combat, family problems, sexual conflicts, prolonged overseas service, difficulty in accepting responsibility, dissatisfaction with the army assignment, and problems in interpersonal relationships with others in the organization. Eighty per

cent of the patients were evacuated to the United States within two months of hospitalization.

On reaching the United States, one-fifth had shown marked symptomatic improvement. After two months of hospitalization, over a third of the patients had been discharged. Only four were continuously hospitalized for more than a year. Comparison of pre-war and post-war adjustments revealed that general health, ability to function at work, family relationships, and social adaptation were all poorer; the sexual adjustment was essentially unchanged. There was a gradual trend toward decrease in disability, though personality deviations characteristic of schizophrenia persisted. After 5 or more years severely handicapping symptoms were present in one-fifth of the patients. Eleven had had further hospitalization. Although the amount of disability compensation had been gradually reduced, over three-fourths of the patients were still receiving some benefits.

The long-term course of the patients studied indicates that schizophrenia in the military service does not differ essentially from that occurring in civilian life. Some schizophrenics functioned in the army for long periods prior to the acute episode despite psychopathologic symptoms. Vulnerability in civilian life to types of stress similar to those encountered in the armed forces indicates that such individuals should not be accepted for military duty. A proper evaluation of assets and deficiencies may lead to better military assignment and lessen the number of psychiatric hospitalizations. A policy of returning soldiers to the United States after a definite period of service overseas may be of use in decreasing the number of psychiatric casualties. The physicians with an understanding of psychiatry may be of great help in preventing and treating psychiatric casualties. Since personality illnesses are a major problem in the military services, whenever it is feasible, special courses or orientation periods in psychiatry should be offered to medical officers. There has been too much emphasis on granting disability compensation and too little on rehabilitation. Continuous treatment efforts can help many with schizophrenia to reach or maintain their best level of adjustment. 6 references, 5 tables.—*Author's abstract.*

234. *Newer Concept of Psychopathic Personalities.* ROBERT B. MILLER, New York N. Y. Dis. Nerv. System *12*:330-37, November 1951.

A review is presented of 50 cases of psychosis with psychopathic personality; 3 nonselected cases are described in detail. The diagnosis of psychopathic personality was made on the basis of accepted criteria. Of 50 cases, 44 were diagnosed as psychotic with a psychopathic state. All except 5 showed formative period factors instilling marked insecurities, even though the child was considered as aggressive and spoiled by relatives. It was impossible from this relatively small series to determine whether overprotection or being thrown on his own resources early was more likely to produce psychopathic behavior. There appeared to be no more hereditary background in this so-called psychopathy than in the general population. Many diagnosed psychoses with psychopathic states, with what seemed like classical symptoms, were shown to have the latter only secondarily.

Of the 3 cases described in detail, one, a 14 year old boy, had had repeated con-

flicts with the law; the second, a man of 33 years of age, was described as vicious; and the third, a man of 50 years,was given to inveterate gambling.

In these cases there were many psychopathic traits, but closer scrutiny revealed deeper determinants as altering their manifest meaning. Regarding sexuality, so-called psychopathic sexuality may be psychopathologic but is not necessarily a psychopathic trait. All of the cases had in common symptoms accepted as being pathognomonic of constitutional psychopathy. Each symptom, regarded from a dynamic standpoint, may be fitted into one or several other diagnostic entities. Cases of dementia praecox, amentias, psychoneurosis, and psychosis with organic disease, all have symptoms, which, if isolated, could also fit into the complex of psychopathy.

With a dynamic approach, the mechanisms behind symptoms are revealed and diagnoses can be revised. In the present series not one of the 50 cases stood up as being psychopathy when the mechanisms were probed. Most so-called psychopaths fall into the diagnosed groups usually more amenable to treatment. A review of medico-legal situations in which the patient was formerly considered as legally sane is urged. With proposed legislation in regard to the "sexual psychopath" this becomes even more important. A plea is offered that symptoms of psychopathy be reconsidered and the patient be re-evaluated as a candidate for treatment as well as for medicolegal purposes.

235. *A Court Clinic for Alcholics. A Dsecription and Evaluation of the Stoughton Clinic.* MARTHA BRUNNER-ORNE, FREDERICK T. IDDINGS, AND JOHN RODRIGUES. Quart. J. Stud. on Alcohol *12*:592-600, December 1951.

The Stoughton Clinic was an experiment initiated in an attempt to deal with alcoholics in a court situation on a local level. The aim of the clinic was to substitute treatment and education for punishment and confinement. Most of the members had been in conflict with the law. The staff included a psychiatrist, a general physician, and the associate director of the Boston Committee on Alcoholism; a psychologist also participated on a volunteer basis. The court officer was a great help and encouraged both prospective and actual members to come to the meetings—frequently bringing them along himself or furnishing transportation.

The physical, emotional, and environmental factors were studied in each case. One frequently has to deal with problems of undernourishment, withdrawal symptoms, occupational, and home situations. The clinic met once a week, and the patients were treated as members not as prisoners. Following the physical examination they were given vitamins and sedatives. At present, sedation has been superseded by administration of tolserol, which provides relaxation without depression or habituation. In some instances the administration of vitamins and tolserol was continued over a period of several months. These patients have to recondition themselves to get along without liquor. During the initial period, antabuse was found helpful in some cases but only when full cooperation was assured. Following the physical examination each member had an interview with the psychiatrist, and these individual interviews were supplemented by group interviews. Voluntary attendance was soon stimulated by the fact that help was offered in obtaining jobs and in straightening out family

problems, economic problems, and legal difficulties. The members also enjoyed the group activities and felt less isolated socially.

Of 32 cases, 16 stopped drinking and became adjusted. It is believed that this project represents the first attempt to establish cooperation between the court and a clinic for alcoholics on a local level. A similar project has been started in New Bedford, Massachusetts, and in Brookline, Massachusetts. The court cooperated by suspending the sentence of an offender who was willing to attend the clinic.

neurology

236. *A Psychiatric, Electroencephalographic and Psychologic Study of Lobotomy in Chronic Schizophrenia.* HARRY ADLER AND DAVID R. TALBOT, Los Angeles, Calif. Dis. Nerv. System *12*:323-29, November 1951.

A study of 38 cases of severe chronic schizophrenia treated by lobotomy showed that proper treatment consists in a follow-up of individualized therapy based on a dynamic approach. The series included 20 paranoids, 11 catatonics, 3 hebephrenics and 4 unclassified cases. Regarding the results of operation 55 per cent of these patients are still in the hospital although considerably improved, 16 per cent are well adjusted in their homes, and 26 per cent unimproved. Three per cent of the cases were considered to be worse than before operation. The degree of postoperative improvement was not related to the age of the patient. From a behavioral aspect, 71 per cent of the patients seemed to be improved following the operation, in spite of retention of many psychological conflicts. Behavior aspects showing marked postoperative changes included aggressiveness, destructiveness (either internalized or externalized), and general motor hyperactivity.

Psychologic symptoms improved in 50 per cent of the cases, affecting hallucinations, delusions (especially delusions of persecution), guilt feelings, and hostility toward parental figures. Grandiose illusions showed no appreciable change and surgery does not relieve feelings of insecurity or inferiority. Some patients appeared to be more dependent following lobotomy, with a feeling of inferiority and loss of self esteem related to the operation, and needed to be repeatedly reassured that they had not lost their intellectual capacity. Two patients died, one failing to survive a second lobotomy, and 3 patients developed convulsive seizures which were controlled with dilantin.

Some of the patients became more timid and fearful following operation and one showed severe regression. The psychologic symptoms changed in degree rather than in form. Hostility persisted, but was less intense and therefore under control. Those with severe guilt obsessions withdrew more than prior to the operation. Reactivation of conflicts brought about a relapse to the same pattern of delusion and hallucination as that present before operation. The electroencephalograms showed that 12-14 per second sleep spindles disappeared in the frontal lobes after lobotomy. In one patient showing a good result of the operation, these spindles had disappeared completely, whereas in a case with poor results the sleep spindles persisted after lobotomy. It is

suggested that deeper and more extensive lobotomies in cases failing to respond to a first lobotomy by disappearance of the sleep spindles may yield better results.

Lobotomy diminishes the affective component of the conflicts with great improvement in behavior and a reduction in psychologic symptoms. Inferiority complexes, fear of environment, erratic behavior and judgment persist and there is diminished anxiety tolerance. Adverse home influences frequently prevent the attainment of best results. In one case, a mother re-awakened feelings of inferiority and guilt, thus bringing on a recurrence of the mental illness. The duration of hospitalization will depend upon the severity of the case and the threats to mental health incident to home surroundings. If the latter prove detrimental, a return of the patient to the hospital in his improved condition should be considered.

After the initial period of confusion is over, the IQ shows an increase of 4 at the end of one month, and of 12 after one year.

Success of lobotomy therefore appears to depend upon a complete severance of connecting fibers leading to the orbital surface and convexity of the frontal lobe. The results will be good if the frontal areas or centers of intellectual ability are cut off from the control of the hypothalamus or center of emotions. 11 references.

237. *Anomalous Horizontal Lamination of Nerve Cells in the Supragranular Cortex of an Idiot Brain.* M. C. H. DODGSON, London, England. J. Neurol, Neurosurg. & Psychiat. *14*:303-07, November 1951.

The central nervous system of an idiot, aged 2¼ years, with generalized spasticity and bilateral downward dislocation of the femora with imperfect acetabular formation, is described. The brain, not grossly malformed, showed internal hydrocephalus without cerebral expansion (skull circumference 44 cm.), the lateral ventricles, interventricular foramina and third ventricle being dilated, although not the aqueduct or fourth ventricle, the lateral recesses being patent.

The second and third layers of prefrontal cortical cells, particularly in the superior frontal region, ran in horizontal rows of single cells parallel to the cortical surface. They had scanty cytoplasm containing little Nissl substance, many being bipolar. In the affected supragranular cortex, there were few nerve fibers, none myelinated and none running horizontally between the rows of cells. There was also reduplication of the dentate gyrus, with absence of normal crowding of pyramidal cells in the *cornu Ammonis*.

The shrunken and gliosed central white matter and corpus callosum were incompletely myelinated, fiber systems tending to run in poorly defined stripes around the ventricles. There was shrinkage and distortion of the thalamus, microscopically showing abortive status marmoratus, with glial fibrosis and irregular myelination. The fornix system was not identified, the mammillary bodies being small, as were the pyramidal tracts.

Comparable, although less definite, horizontal lamination of prefrontal cortical cells was seen in a premature infant of 26 weeks gestation, but does not occur in the full term infant (Conel). The anomaly may therefore be the exaggerated persistence of a prenatal arrangement. Hydrocephalus probably arose *ex vacuo* from shrinkage

following a prenatal anoxic or toxic process, with, possibly, diffusion of a toxic substance from the ventricles. Both cortical anomaly and white matter lesion were probably expressions of a single pathologic process. 13 references. 5 figures.—*Author's abstract.*

238. *Electroencephalography in a General Hospital. Resume of 500 Records.* ALEX J. ARIEFF, Chicago, Ill. Quart. Bull., Northwestern Univ. M. School *25*:342-44, Winter 1951.

In a review of approximately 500 EEG records, various correlations were attempted with clinical syndromes or reason for examination.

In 204 records of patients with epilepsy, 80 per cent were considered abnormal, but in only 41 patients, or 20 per cent, were spike wave complexes found (this being practically diagnostic of epilepsy). In the 41 patients, 11 had minor seizures, 20 had major seizures and in 10 both types were present.

In 75 suspected brain tumors, only 18 were verified at operation or autopsy. Of these, in 5 or 23 per cent, there was a slow wave focus. In 3 there was diffuse spiking, including one with spike wave discharge. In one there was a spiking focus and 2 showed amplitude asymmetry (one had the decrease on the involved side and the others on the normal side). These records were abnormally slow and 4, or 20 per cent, were normal.

In 44 patients with fainting or syncopal spells, convulsions were noted in 5 and questionable in 3. In 17, or 32 per cent, the record was normal (in spite of 2 with convulsions).

Abnormalities were noted in isolated instances in manic depressive psychosis, headaches, migraine syndrome, Menière's syndrome, schizophrenia, and senile dementia.

Of 15 patients with cerebral apoplexy, 66 per cent were abnormal, possibly due to a high incidence of associated convulsive states.

In 20 patients with dizzy spells, the majority were normal. Those with abnormalities must be further investigated as having convulsive or organic brain disease backgrounds.

In cerebral trauma, the majority showed abnormalities and their improvement could be followed over a period of time.

In an EEG laboratory, the majority of cases will consist of abnormalities, inasmuch as most patients sent for examination will be allied to the epileptic states. 1 table.—*Author's abstract.*

239. *Acute Psychic Disturbances Following Operations on the Brain (Acute Psykische Störungen als Hirnoperationsfolgen).* JOACHIM-ERNEST MEYER AND LOTHAR WITTSKOWSKY, Freiburg, Switzerland. Arch. f. Psychiat. *187*:1-38, 1951.

Only 15 per cent of a series of 60 cases of brain surgery failed to show transitory psychic disturbances following the operation. Symptoms usually developed on the second to fourth day after the intervention and consisted of confusion in 26 cases,

with amnesia in 12 cases and delirium in 4 cases. Orientation was impaired especially at night when vision was poor. Postoperative delirium occurred in 2 cases of pituitary adenoma, 1 craniopharyngioma and 1 large frontal lobe glioma. The delirium corresponded to the usual type observed in symptomatic psychoses. Retrograde amnesia was present in 5 instances. Postoperative changes in drive appeared (1) as increased drive during the intra-operative manic state, (2) as diminished drive in confused states, and (3) as marked diminution of drive in 3 cases with clear mentality and no frontal involvement. Other disturbances noted included incoherent thinking in delirium, flighty states in the intra-operative manic reaction, and general retardation of mental processes in confused or apathetic patients. One patient displayed a transitory paranoid disturbance. Aside from the common organic euphoria, a change in mood as a result of the operation was observed only in the intra-operative manic syndrome. Only one patient passed through a short period of depression following the operation. Most various optical delusions were frequently associated with the confused state, but occurred also in the absence of the latter. Acoustic and sensory disturbances occurred only in states of delirium. Transitory manic disturbances developed during operation in 7 patients. With one exception, the operation in these cases involved the frontal lobes, or the frontal route to gain access to basal tumors.

In 2 operations in the vicinity of the midbrain, and 1 sudden evacuation of a hydrocephalus, a prolonged soporific state developed during the operation. On the other hand, in one patient, the sudden evacuation of a cystic craniopharyngioma, produced a soporific state lasting for a whole day. Marked insomnia was observed in some cases of operation in the vicinity of the midbrain. In 2 cases attacks of inverted vision were observed following operations on the posterior cranial fossa.

The most severe psychic disturbances occurred during the stage of postoperative cerebral edema. Apparently, increase in intracranial pressure, per se, will not suffice to produce the psychic disturbances here described. Transitory postoperative neurologic symptoms or facial edema indicated the presence of cerebral edema. 67 references.

ophthalmology

240. *The Magnitude of the Pulfrich Stereophenomenon as a Function of Distance of Observation.* ALFRED LIT AND AARON HYMAN, New York, N. Y. Am. J. Optom. & Arch. Am. Acad. Optom. *28*:564-81, November 1951.

This investigation is a continuation of a seven point research program concerned with the Pulfrich stereophenomenon. An oscillating target appears to rotate out of its plane of oscillation when binocularly observed under conditions of unequal retinal illumination. The apparent displacements are attributed to differences in the visual latent periods for the two eyes, resulting from the differential retinal illumination. Appropriate theory allows for calculation of latency differences when the near and far displacements in the vertical median plane are determined experimentally.

Data for a practiced subject are presented in tabular and graphic form, indicating

the magnitude of the near and far displacements (and the corresponding calculated latency differences) produced by seven differences in retinal illumination, at each of six distances of observation, ranging from 30 cm. to 150 cm.

A specially designed apparatus provides an oscillating target which executes constant linear motion in a frontal plane to produce an identical angular velocity at the subject's eyes for all distances of observation. The angular extent of stroke and the angular size of the oscillating target are maintained constant for all testing distances.

The experimental results are consistent with those predicted from the theory and geometric analysis of the Pulfrich stereoeffect. For any of the given differences in retinal brightness, the magnitude of the stereoeffect varies with distance of observation to produce a constant calculated latency difference. Minor discrepancies between theoretical and experimental results are discussed.—*Author's abstract.*

241. *Why Wear Glasses (Pourquoi porter des verres)?* J. R. POIRIER, Canada. L'Union Médicale du Canada *80*:1197-1208, October 1951.

In this article Poirier describes the regular refractive errors—how those errors affect visual acuity and the visual comfort of the patient. He describes accommodation and discusses how errors of refraction affect the accommodation necessary for various visual tasks. He also discusses the progressive diminution of accommodation with age and the effect of that change on the ability of the patient to do close work.

Due to the severe tasks imposed on the eyes, as a result of our present civilization, the limits of the refractive error of the normal eye can be considered to be + 1.00 diopters and —0.50 diopters. While the refractive errors affect vision or change the amount of accommodation which is available, they cannot be considered to indicate any disease of the eye.

There are three major reasons for wearing glasses: to sharpen blurred vision, to decrease ocular fatigue, or to allow a patient to achieve some difficult task which our present civilization imposes.

The article is well written, interesting, and might be of value to medical students and general practitioners.

242. *Eyelessness in Cave Animals.* ARTHUR SHLAIFER, Philadelphia, Pa. Am. J. Optom. & Arch. Am. Acad. Optom. *28*:534-43, October 1951.

The results of anatomic studies on the eyes of cave fish are discussed. In addition to totally blind forms of the Mexican cave fish, *Anoptichthys jordani*, there exist intermediate forms of the same species with less complete ocular degeneration and with some visual responses, such as striking at food particles.

Relative degree of blindness is correlated, to a degree, with relative lack of body pigmentation. The behavior of blind cave fish, with reference to sensitivity to light and the results of studies on the effect of prolonged darkness on the vision of normal-eyed related species, are described. Whether the blind forms lost their visual equipment after entering the caves or whether a mutation with defective vision entered the caves and survived is a speculative question. Factors leading to eyelessness and the evolutionary implications of eyelessness in cave fish are presented.—*Author's abstract.*

book reviews

Biological Antagonism. The Theory of Biological Relativity. GUSTAV J. MARTIN. Philadelphia, Blakiston Co., 1951. 516 pp. Price $8.50.

This is a thoroughly complete, yet concise, presentation of the theory of biologic relativity—that "general law" which underlies all biologic activity and is fundamental to the resolution of all problems in biology.

The author reviews biologic antagonism as reflected in natural and synthetic displacing agents, covers antagonism as seen in the fields of amino acids, purines, pyrimidines, vitamins, hormones, minerals, and as it forms the basis of immunology, pharmacology, and chemotherapy. Finally, he offers the concept of biologic relativity based upon extensive study of these antagonisms.

Research workers in immunology, pharmacology, chemotherapy, medicine, and the entire field of biology will find the references throughout the book extremely helpful. Carefully selected by the author because of their pertinence to the subject, they present a comprehensive survey of all the literature in the field.

The Cost of Sickness and the Price of Health. C.-E. A. WINSLOW. World Health Organization: Monograph Series, No. 7. 106 pp. Price $1.50.

The keynote of the study is that "prevention is not only better than cure; it is also cheaper." The relatively small investment involved in a sound public-health program is contrasted with the "staggering burden upon the human race" imposed by the cost of preventable diseases. The economic burden of many diseases in a number of countries is discussed on the basis of impressive data, with the conclusion that "Every step that can be taken toward lessening this burden will not only diminish suffering and prolong human life; it will also increase productivity and promote prosperity. This prosperity, in turn, must not be considered as an ultimate end in itself. If wisely conducted, economic improvement may make it possible for peoples . . . to enjoy a fuller and a richer existence."

The study outlines the various methods of reducing the burden of disease and the economic results thus obtained. General indications are given of the cost of planning a national health service and of the needs it would meet. The worldwide program of co-operative assistance, a program which, to the historian of the future, "may well seem . . . one of the most brilliant and outstanding contributions of the 20th century to world history," is outlined and discussed.

The problem of health cannot, however, be solved by the public-health worker alone. It is not enough "for the health administrator to develop the soundest possible program for his own field of social endeavour . . . He must also sit down with experts on agriculture, on industry, on economics, and on education and integrate his specific health program as a part of a larger total program of social reconstruction."

Professor C.-E. A. Winslow, the author of the study, is one of the foremost authorities in public health, and through his pioneer work has come to exercise a great influence on the medical and public-health professions.

news

RENE DUBOS RECEIVES HIGH SCIENCE AWARD

Dr. Rene J. Dubos, world-famous authority on tuberculosis, has recently received the 1952 annual Research Award of the American Pharmaceutical Manufacturers' Association for scientific contributions to the "welfare of mankind."

The award citation hailed Dr. Dubos as "perhaps the greatest authority on the bacteriology, immunology and biochemistry of the bacillus of tuberculosis." The French-born scientist's research work in this country over the past quarter-century resulted in the discovery of two antibacterial substances, designated tyrothricin and gramicidin, which led to the development of penicillin and streptomycin.

A full Member of the Rockefeller Institute for Medical Research, his interest in microbiology was first aroused in 1922 when he was assistant editor on the staff of the International Institute of Agriculture, in Rome. He came to the United States in 1924 and became associated with Dr. Selman Waksman at the New Jersey Agricultural Experiment Station. After obtaining his Ph.D. degree here in 1927, he joined the Rockefeller Institute and rose from Fellow to his present position of Member.

From 1942 to 1944 he was George Fabyan Professor of Comparative Pathology and Professor of Tropical Medicine at the Harvard Medical School, then resumed his post at the Rockefeller Institute.

STRUCTURE OF GROWTH FACTOR SOLVED

The chemical structure of a recognized growth factor, which is needed by many micro-organisms, is described for the first time in the current issue of the Journal of the American Chemical Society. Research workers at Lederle Laboratories solved the molecular structure and synthesis of what has been named "thioctic acid."

The growth factor, originally termed "Protogen," was first described by Professor G. W. Kidder and Dr. Virginia Dewey of Amherst College in 1944, and since then there has been a heated race among a number of research teams to solve its structure.

The function of thioctic acid in nutrition is not fully understood, but it is known to form part of an enzyme system needed for the oxidation of carbohydrates in tissues of higher animals. It is related to the B-complex vitamins and is found in liver. Over 100 tons of liver were concentrated to obtain only a few milligrams of this growth factor for chemical studies. The molecule was found to contain two atoms of sulfur and the remainder was composed of carbon, hydrogen and oxygen.

Eventually the active chemical was synthesized, using furyl-acrolein, a corn cob derivative, as a starting material. The new substance was named thioctic acid as a short description of its chemical name, dithio-octanoic acid.

Thioctic acid is so powerful, report the Lederle scientists, that one part can be detected in 10 billion parts of culture medium by a test with micro-organisms.

Although no use for the new substance has yet been revealed, it is expected to be of value in studies of the chemistry of living tissues.

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Riboflavin (B_2, G)	1.0 mg.
Nicotinamide	8.0 mg.
Pyridoxine Hydrochloride (B_6)	0.5 mg.
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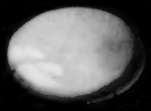
Easily swallowed, sugar-coated Terramycin Tablets introduce new flexibility in prolonged courses of administration and are particularly suited to effective, well tolerated therapy among patients preferring tablets to other oral forms.

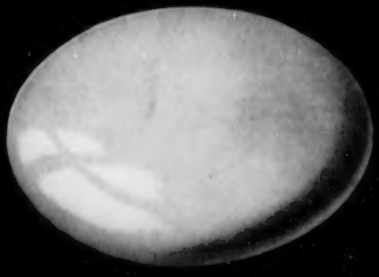
Supplied: 250 mg. tablets, bottles of 16 and 100; 100 mg. and 50 mg. tablets, bottles of 25 and 100



Terramycin tablets

SUGAR-COATED

AMPHOTERIC



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